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MEGALOBLASTIC ANEMIA IN INFANCY

A Common Syndrome Responding Specifically to Folic Acid Therapy

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THIS report, based on a detailed study of 25 patients,[1] deals with a macrocytic anemia of common occurrence in infancy which hitherto has eluded a clear definition and has often escaped recognition altogether. The nature of this condition, which, for reasons stated later, we shall call megaloblastic anemia, has remained obscure and its diagnosis uncertain because the pathogenic mechanism has been studied by inadequate methods, unreliable hematologic criteria have been used, a uniform clinical picture is lacking and the response to therapeutic agents such as liver extract, therefore, has seemed inconsistent and unpredictable.

We shall endeavor to define this condition as a pathogenetic entity rather than as a disease of uniform causation. Like several other types of anemia, it represents a syndrome which can be induced by a variety of causative factors but is produced always by the same mechanism and reflects a specific disturbance in the physiology of the blood-forming organs. This syndrome is the result of a specific dysplasia and dysfunction of the bone marrow organ developing in the absence of an essential hemopoietic principle and leading to a severe anemia. It can be recognized by characteristic morphologic changes in the marrow cells and responds specifically and predictably to folic acid as well as to liver extract.

For the sake of convenience this report is divided into four sections. In the first part, we outline the clinical features and show the results of therapy in our cases, with only brief reference to the blood and bone marrow picture for purposes of orientation. In the second part we deal with the morphologic changes in the hemopoietic apparatus and the

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1. Zuelzer, W. W., and Ogden, F. N.: Response to Folic Acid in Megaloblastic Anemia of Infants: Preliminary Report, Proc. Soc. Exper. Biol. & Med., to be published.

alterations in the blood reflecting these changes. With the help of the diagnostic criteria thus established, we analyze our results in part three and attempt to demonstrate the specificity both of the marrow lesion and of the therapeutic response. This enables us to consider in the fourth part of this study the pathogenesis of the anemia, to define it on a physiologic basis, to analyze the etiologic factors and to establish the syndrome as an entity among the various conditions associated with macrocytosis of the blood.

MATERIALS AND METHODS [1a]

Our clinical material [2] consists of the cases of 25 patients admitted without selection during a period of sixteen months, with the exception of 1 case (case 21) in which sufficient data for exact classification happened to be available although the patient's admission preceded our study by several years. Only cases of infants under 18 months of age were included in the study.[2a] It was thought best to exclude from this report a considerable number of apparently similar cases seen in our clinic before the present diagnostic criteria were developed.

The patients were studied in the following manner: hemoglobin levels, red blood cell counts and white blood cell counts were determined daily in the usual way, the photoelectric method of Evelyn being used for hemoglobin determinations, with standards based on oxygen capacity as found with the Van Slyke apparatus. Daily reticulocyte counts were done by the "dry" method. Frequent platelet counts were done by the Fonio method, chamber counts with Rees-Ecker fluid being used for occasional checks. The study of blood films was considered sufficiently accurate for comparative purposes and was relied on for day to day evaluation of the number of platelets. Hematocrit readings were determined by centrifuging blood obtained by venipuncture for thirty minutes at 2,500 revolutions per minute.

Price-Jones curves were constructed by projecting stained blood films onto transparent paper, on which the erythrocytes sharply in focus were traced and later measured with a scale constructed from equally magnified projections of a micrometer slide. Controls of normal adult blood served to establish the degree of shrinkage for standards of comparison.

1a. Since the manuscript was submitted, 4 additional cases were studied, 2 through the cooperation of Dr. James L. Wilson, of the Department of Pediatrics, University of Michigan. The observations in these cases and the results of folic acid therapy support in every respect the conclusions presented in this paper.

2. Folic acid concentrate, "L. casei factor," extracted from liver and said to contain 1 mg. of folic acid per cubic centimeter in liquid form and 0.45 mg. per capsule in dry powdered form, as well as "synthetic folic acid," was supplied through the courtesy of Dr. B. W. Carey, of Lederle Laboratories, Inc. For therapeutic purposes, the liquid concentrate was mixed with the infant's formula. The powdered concentrate and the pure folic acid when given orally were stirred into the formula, sweetened with saccharin and taken by the infants without much difficulty. For intramuscular injection, the synthetic folic acid was dissolved in isotonic solution of sodium chloride made alkaline by buffering to a p_H of 8.0 and sterilized by passage through a Seitz filter. Purified liver extract (15 units per cubic centimeter) was obtained from Lederle Laboratories, Inc. The crude liver extract (2 units per cubic centimeter) was purchased from Eli Lilly and Company.

2a. During this sixteen month period 1,656 infants under 18 months of age were admitted to the wards of the Children's Hospital.

The icterus index and the serum protein were determined in most cases, if possible, before transfusion.

Examinations of the urine were done in the routine manner, and occasional rough quantitative tests for urobilinogen were performed. Quantitative analyses of the urobilinogen content of the stools were omitted because of difficulties in obtaining samples.

Gastric analyses were performed in 10 cases. Blood for culture was taken when indicated and stools were cultured in nearly every case. The Mazzini microflocculation test was used to exclude syphilis, and in 16 cases agglutination tests for enteric pathogens and the Brucella group of organisms were performed.

Roentgenograms were made of the chest, skull and long bones.

Aspirations of bone marrow were done with the Turkel needle before treatment was begun and repeated at least once, usually at the height of the reticulocyte response but sometimes earlier or later as indicated. The usual site of aspiration was the lower end of the femur, because femoral marrow is easily accessible in infants and its use permits the withdrawal of larger amounts suitable for volumetric studies. Heparin was used as an anticoagulant, and a modification of Schleicher's method [3] was used for the study of the marrow elements. Smears made from the buffy coat of the marrow after centrifugation were dried quickly by air and stained with various Romanovsky stains, notably May-Grünwald-Giemsa stain and occasionally Goodpasture's peroxidase stain.

After discharge from the hospital, the patients were followed in the Anemia Clinic at frequent intervals, and hematologic studies were repeated as often as indicated.

In all fatal cases autopsies were performed. The observations will be commented on in a separate communication.[3a]

In addition to the studies on the patients, examinations of the blood of the mothers were made, and in 1 case aspiration of sternal marrow and gastric analysis were performed on the mother.

I. CLINICAL OBSERVATIONS

Observations on Admission.—The data summarizing the histories and results of examination at the time of admission are given in table 1. A uniform clinical picture was lacking, except for symptoms referable to the anemia, such as pallor, weakness, loss of appetite and irritability. The patients were all white infants ranging from 2 to 16 months of age. A few of them were born prematurely. The sexes were evenly distributed in the group. Most of the infants had cough, coryza or both for several weeks before admission, and the beginning of the illness was usually referred to the onset of these symptoms. In 2 instances the illness had begun with chickenpox; in a third it followed whooping cough. Fever, vomiting and diarrhea were common complaints. In several cases petechiae had been noted by the parents, and in 1 instance icterus was the leading symptom.

3. Schleicher, E. M.: The Volumetric Pattern of Aspirated Normal Human Sternal Marrow of Males 18 to 40 Years, Am. J. Clin. Path. **14**:370, 1944.

3a. Zuelzer, W. W.: The Pathology of Megaloblastic Anemia in Infancy, to be published.

The physical observations on admission were related chiefly to the existence of a severe anemia. Extreme pallor was the outstanding feature. Frequently a soft systolic murmur could be heard over the precordium, and slight cardiac enlargement was evident. The liver was invariably increased in size, but the spleen was palpable in only 10 of the patients. In no case was there any appreciable lymphadenopathy.

TABLE 1.—*Summary of* [illegible] *es of th*

			History				
Case	Age, Mo.	Birth	Past History	Chief Complaint	Fever	Pallor	Anorexia
1	12	Term	Otitis	Pallor 3 wk.	+	+	+
2	12	Term	Chickenpox at 9 mo.	Vomiting, pallor, diarrhea	?	+	?
3	4	Premature	.....	Diarrhea, pallor	—	+	—
4	9	Term	Cough 1 mo.	Stomatitis	—	+	+
5	9	Term	Stomatitis at 6 mo.	Vomiting, pallor	?	+	+
6	9	Term	"Collapsed lung" 3 wk.; pneumonia, stomatitis at 7 mo.	Pallor since birth	+	+	—
7	2	Term	.....	Heavy breathing	+	?	+
8	4	Premature	"Kidney infection"	Vomiting, pallor	?	+	?
9	11	Term	.....	Weight loss	?	—	+
10	8	Term	.....	Pallor, vomiting	+	+	+
11	11	Term	Chickenpox at 9 mo.	Vomiting, weight loss 2 mo.	?	+	—
12	3	Term	Jaundice at birth	Pallor 4 wk.	—	+	+
13	11	Term	Sore throat at 7 mo.	Rapid breathing	+	—	+
14	9	Term	.....	Anorexia, "run down"	?	+	+
15	5	Term	.....	Pallor, colds	—	+	+
16	16	Term	Cough at 1 yr.	"Run down"	+	—	+
17	4	Term	.....	Pallor, cold	—	+	—
18	2	Premature	.....	Anemia	?	+	?
19	3½	Premature	.....	Vomiting, weight loss, abdominal distention, fever	+	+	+
20	2½	Premature	Slight upper respiratory infection at 9 wk.	Petechiae, fever, anemia	+	+	—
21	13	Term	Many colds	Drowsiness, anorexia	?	?	+
22	8	Term	Many colds	Weight loss	+	?	—
23	7	Term	"Always pale"	Fever	+	+	+
24	8	Term	.....	Nosebleed	—	?	—
25	9	Term	"Always pale"	Anemia	+	+	+

Petechiae in the skin were noted in 5 of the patients. The nutritional state as revealed by weight was poor in over half of the group but satisfactory in the remainder. Six of the patients had clinical signs of scurvy. In 19 patients fever of variable degree was present. A few infants had evidence of pneumonia; 1 patient had otitis media, and 2 others had stomatitis. In 2 patients abdominal distention was prominent. One infant exhibited pronounced icterus, which at autopsy was found to be the result of a severe hepatitis.

Roentgenograms of the skeleton, apart from confirming the clinical impression of scurvy in 6 cases, revealed generalized osteoporosis in 5 additional instances. In 2 cases widening of the medullary spaces of the long bones was also noted.

Laboratory Data.—The essential laboratory data are given in table 2. The anemia was usually severe and normochromic-macrocytic in type.

...s of the Time of Admission

			Physical Examination					
Evidence of Upper Respiratory Infection	Other Symptoms	Duration	Hepato-megaly	Spleno-megaly	Petech-iae	Nutritional State	Other Conditions	Roentgen Examination
+	—	1 mo.	+	—	—	Poor	.....	Normal
+	—	3 mo.	+	—	—	Poor	Ulcers on tongue, otitis	Osteoporosis
+	Apathy	6 wk.	+	+	—	Poor	.....	Osteoporosis
+	Apathy	1 mo.	+	+	—	Fair	.....	Normal
+	—	1 mo.	+	—	—	Poor	Scaling skin	Scurvy; osteo-porosis
+	—	1 mo.	—	+	—	Poor	.....	Normal
+	Convulsions	2 wk.	+	+	—	Fair	Pneumonia, post-nasal drip, carpo-pedal spasm	?
+	—	1 mo.	+	+	+	Fair	.....	Osteoporosis
+	Weight loss, apathy	4 mo.	+	—	+	Poor	Bleeding from ears, nose mouth	Osteoporosis
+	—	1 mo.	+	—	+	Fair	Hemorrhage soft palate	Normal
+	Bleeding, tender gums	2 mo.	—	—	+	Poor	Bleeding gums	Scurvy, osteo-porosis
—	—	4 wk.	+	+	—	Fair	.....	Normal
+	Hyperpnea	4 mo.	+	—	—	Poor	Pneumonia, pharyngeal ulcers	Scurvy
+	Weak	1 mo.	+	—	—	Poor	.....	Scurvy, osteo-porosis
+	Otitis	1 wk.	—	—	—	Fair	Perforation right ear	?
+	—	6½ mo.	+	+	—	Poor	Pneumonia	?
+	—	1 wk.	+	+	—	Fair	.....	Normal
—	Icterus	1 mo.	+	+	—	Fair	.....	Osteoporosis
+	Dehydration, distention	3 wk.	+	—	—	Poor	.....	Normal
—	Restlessness	2 wk.	+	+	+	Poor	Otitis media	Normal
+	Apathy	6 wk.	+	—	—	Good	Coma	Osteoporosis
+	—	5 mo.	—	—	—	Poor	.....	Osteoporosis
+	—	2 wk.	+	—	—	Poor	Scaling skin, otitis media	Scurvy
—	Hyperpnea	2½ mo.	—	—	—	Good	Bronchitis	Svurvy, osteo-porosis
+	Apathy	1 mo.	+	+	—	Good	Mongolism	Normal

The bone marrow pattern was megaloblastic. These observations will be discussed in detail later. The frequent occurrence of a histamine refractory achlorhydria was of interest. The serum protein tended to be low. The icterus index was often slightly elevated in patients without clinical jaundice. Routine examinations of the urine showed no significant abnormalities in any of the patients. Cultures of stools and results of tests for agglutination against enteric pathogens were negative with 1 exception (case 23).

TABLE 2.—*Summary of Pertinent Laboratory Data on Admission*

Case	Hemoglobin, Gm./100 Cc.	Red Blood Cells, Millions	Color Index	Hematocrit, %	Mean Corpuscular Hemoglobin, Concentration, %	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Volume, Cubic Microns	White Blood Cells	Polymorphonuclears, %	Platelets	Reticulocytes, %	Bleeding Time, Minutes	Clotting Time, Minutes	Icterus Index, Units	Serum Protein, Gm./100 Cc.	Gastric Acidity, Units	
																Free	Total
1	3.1	0.89	1.2	10.5	29.5	34.9	118	8,300	49	Diminished	0.3	..	..	6.8	6.16	..	..
2	3.5	1.12	1.07	....	....	31.3	...	4,900	24	Diminished	0.4	..	..	12	5.47	..	12
	5.6*	1.86*	1.0	15*	37	30.8	80.6										
3	6.6	2.41	0.9	23	29	27.4	95.5	10,000	23	Diminished	1.4	..	..	2	5.47	0	6
4	4.1	1.0	1.4	12	34	41	120	8,150	20	25,000	0.9	12.5	2	..	4.78	5	13
5	5.0	1.12	1.5	15.5	32	44.6	138	12,550	23	163,960	2.7	3.5	6	6	6.05	0	58
6	4.3	1.14	1.3	13.2	32.6	37.7	116	7,100	38	79,800	0.7	6.25	4.3	8	4.78	..	..
7	6.2	2.05	1.0	18.2	34.1	30.3	89	9,150	23	71,200	2.2	..	..	4.2	4.45	..	..
8	3.3	1.07	1.1	10.5	31.8	30	98	6,500	35	14,980	4.9	..	..	27	4.78	0	16
9	2.7	0.84	1.07	7.3 (?)	37 (?)	31.1	87 (?)	4,500	66	206,000	2.5	..	..	37.3	4.8	..	..
10	4.5	1.4	1.1	....	....	32.1	...	2,200	27	11,000	0.5	..	..	10	....	0	56
11	5.9	1.81	1.13	....	....	32.6	...	16,100	36	Diminished	2.1	..	..	5	5.5	0	4
12	3.3	0.97	1.17	7.0	47	34.0	72	7,750	1	Diminished	1.7	4	4.5	..	5.47	0	4
13	4.1	1.44	1.01	14.0	29.4	28.5	97	7,150	48	Diminished	0	10	4	10	4.78	..	..
14	4.1	1.44	1.01	....	....	28.5	...	4,900	34	Absent	1.9	..	..	..	4.45	..	..
15	6.5	1.88	1.2	....	....	35	...	4,040	36	Diminished	0.2	..	..	7	6.5	..	..
16	5.1	1.27	1.4	18	28	40	142	6,800	21	Diminished	0.1	..	..	..	....	..	..
17	4.4	1.60	1.0	....	....	28	...	5,950	22	119,900	4.8	..	..	13	....	..	..
18	5.5	1.54	1.2	24 (?)	23 (?)	36	156 (?)	12,700	33	60,000	0	..	..	98	4.78	..	..
19	4.3	1.32	1.1	14	30.8	32	106	7,850	19	299,080	2.3	..	..	23	....	..	..
20	3.9	1.47	0.9	....	....	26.6	...	18,950	8	13,000	1.4	..	..	19	....	..	..
21	12.4*	4.05*	1.04	....	....	30.6	...	11,400	61	Diminished	...	..	..	Icterus	....	..	..
22	5.1	1.51	1.2	16	32	33	106	6,250	28	Diminished	3.7	..	..	16	5.12	..	..
23	4.5	1.88	0.8	14.3	31.5	24	76	12,150	14	Diminished	1.1	..	..	..	....	..	..
24	5.4	2.05	0.9	18	30	26	88	8,400	42	Normal	2.9	14	3.75	7	5.42	0	6
25	5.8	1.60	1.21	18.5	31.4	36.6	116	8,500	35	8,000	7.1	5.75	3.5	13	5.47	0	2

* = after transfusion; (?) = questionable accuracy.

Course.—The course of the patient's hospital stay varied from case to case. At first the anemia usually overshadowed the clinical picture and had to be considered first in the treatment, but in most cases it ceased to be the main problem within a short time after therapy was begun. The course then became that of the underlying or associated condition or of complications, such as diarrheal disease, pneumonia, hepatitis, meningitis, subarachnoid hemorrhage, septicemia or renal disease. In some cases the outstanding feature was a protracted irregular fever, for which an adequate explanation could not be found.

Results of Therapy.—Table 3 summarizes the treatment given to the 25 patients and the responses obtained. For our present purpose we are concerned solely with the effects of therapy on the anemia. Associated conditions or complications, even though fatal in some cases, will

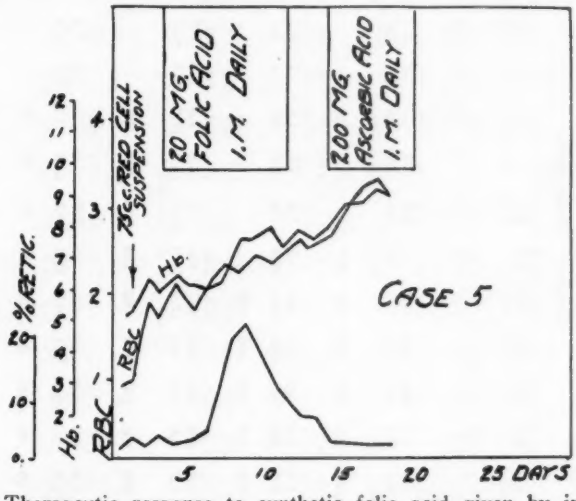

Fig. 1.—Therapeutic response to synthetic folic acid given by intramuscular injection. Antiscorbutic therapy was withheld until the response to folic acid was evident. Note the lack of reticulocyte response to ascorbic acid.

be considered only in so far as they directly or indirectly influenced the state of the blood.

In every case in which the results of treatment could be followed over a sufficient period and were not obscured by the effects of transfusions, folic acid or liver extract had a distinct curative effect. The effect of folic acid was not distinguishable from that of liver extract, regardless of the type of preparation of the latter or the mode of administration. Beginning between the third and the fourth day, the reticulocytes in the blood began to rise, and shortly afterward the hemoglobin level and the red blood count began to improve (fig. 1). The reticulocytosis usually reached a peak of considerable proportions in another three to four days and then decreased rapidly while the hemoglobin

TABLE 3.—*Summary of Therapy*

	Administration	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Comment
Group I (Folic Acid)																						
Case 1	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		4.2	3.1	2.9	4.5	5.0	5.4	6.2	5.7	5.8	5.8	....	6.1	6.2	6.1	7.4	7.3	7.5	....	8.8	8.4	Uncomplicated recovery;
Reticulocytes, %		....	....	0.3	....	....	1.3	0.3	0.3	....	1.2	8.1	17.6	17.5	23.6	14.9	3.1	12.1	....	0.5	1.8	no further effect of folic
Therapy:																						acid or purified liver ex-
Transfusion, cc.		...	...	100	...	60																tract; hemoglobin 10.4 Gm.
Folic acid conc., mg.	Oral	..	..	..	..	..	..	..	5	5	5	5	5	5	5	5	5	....	....	....	5	on 26th day; well 6 months later
Case 2	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		3.5	5.6	5.8	5.3	5.2	6.5	6.8	6.9	....	7.6	7.4	7.5	7.9	8.0	7.8	8.4	8.2	8.1	8.4		Uncomplicated recovery;
Reticulocytes, %		....	0.4	0.4	0.2	0.3	1.2	3.5	9.6	8.2	7.3	5.9	8.8	6.3	3.8	2.1	1.4	0.6	0.4	4.3		slight reticulocytosis(4.3%)
Therapy:																						4 days after second course
Transfusion, cc.		60																				of folic acid; hemoglobin
Folic acid conc., mg.	Oral	....	....	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0									10.4 Gm. on 30th day; well 6 weeks later
Case 3	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		7.8	6.6	7.1	7.0	7.1	6.9	6.8	6.4	7.1	7.5	7.8	7.9	9.2	9.5	9.5	9.5	9.4	9.5	9.8	10.0	Uncomplicated recovery;
Reticulocytes, %		....	1.4	1.8	2.4	2.0	2.2	14.0	21.1	18.8	7.4	7.6	8.2	....	5.7	5.5	3.6	3.2	2.9	3.2		no further effect of folic
Therapy:																						acid or liver; no follow-up
Synth. folic acid, mg.	Oral	....	....	....	100	100	100	100	100	....	....	....	....	....	....	....	....	....	....	100	100	
Case 4	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		4.1	6.8	5.9	5.4	6.0	6.5	6.6	6.7	6.5	7.4	6.8	7.6	8.8	8.8	8.6	8.8	9.3	8.8	8.7	8.6	Uncomplicated recovery;
Reticulocytes, %		0.9	1.2	2.0	1.7	3.0	2.8	6.2	12.9	26.0	20.2	13.2	12.6	13.4	14.0	10.8	12.0	10.8	9.1	10.4	9.7	received iron therapy
Therapy:																						later; hemoglobin 9.3 Gm.
Transfusion, cc.		40*																				32d day; well 1 month
Synth. folic acid, mg.	Oral	....	....	....	100	100	100	100	100	100	100	100	100									
Case 5	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		5.0	5.2	6.4	5.8	6.5	6.0	5.9	6.1	7.5	7.6	7.9	7.0	7.8	7.4	7.8	8.8	8.6	9.0	8.8	8.8	Active scurvy; ascorbic
Reticulocytes, %		2.7	3.1	2.7	3.0	2.3	3.0	6.4	16.1	23.3	18.3	13.4	9.3	7.1	6.4	2.0	2.0	2.2	1.9	2.3	1.1	acid (200 mg.) I. M. daily
Therapy:																						after 15th day; no further
Synth. folic acid, mg.	I. M.	....	....	....	20	20	20	20	20	20	20	20	20									reticulocytosis; clinically
																						well at discharge
Case 6	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	
Hemoglobin, Gm.		5.0	4.3	7.0	7.0	7.0	6.4	7.1	6.6	6.9	7.6	6.5	6.7	9.1	9.6	9.4	8.8	9.9	9.3	8.6	8.3	Continuous fever after 9th
Reticulocytes, %		....	0.7	6.6	4.6	4.1	11.3	12.3	10.8	22.0	11.6	10.2	6.4	1.1	1.5	1.7	2.1	3.7	3.1	3.3	2.7	day; chronic basal menin-
Therapy:																						gococcus meningitis; not
Transfusion, cc.		....	100*	....	....	....	....	....	....	....	....	....	100									responding to sulfadiazine
Synth. folic acid, mg.	Oral	....	100	100	100	100	100	100	100	....	100	100	100	100								or penicillin; no response
																						to 2d course of folic acid

Case 7																						Anemia developed while under treatment for acidosis; death on 20th day in uncontrollable acidosis; autopsy—calcification of renal tubules; cerebral softening
Hemoglobin, Gm.		9.1	....	....	....	7.4	8.4	....	....	6.2	6.2	6.0	5.9	4.5	6.0	6.5	6.6	7.2	7.5	8.3	6.9	
Reticulocytes, %		....	....	....	....	....	....	....	....	....	2.2	1.5	0.9	1.6	3.3	5.9	4.1	4.6	3.9	3.5	3.3	
Therapy:																						
Transfusion, cc.		....	....	....	....	....	....	....	....	....	....	....	....	50*								
Synth. folic acid, mg.	I. M.	....	....	....	....	....	....	....	....	....	....	50	50	50	50	50	50	50	50	50	50	
Case 8																						Massive bilateral pneumonia developed despite sulfadiazine and penicillin; died 14th hospital day; autopsy confirmatory
Hemoglobin, Gm.		4.1	3.3	5.5	7.5	8.1	....	6.2	5.6	5.2	4.5	6.0	5.0	5.2	4.7							
Reticulocytes, %		....	4.9	4.6	2.8	3.1	2.9	2.8	2.0	2.4	2.0	0.8	1.1	1.0	2.5							
Therapy:																						
Transfusion, cc.		....	50*	40*	....	....	....	....	....	....	30*	....	....	....	60							
Synth. folic acid, mg.	Oral	....	....	....	....	....	....	....	....	....	....	....	....	100	100							
Crude liver ext., units	I. M.	....	....	....	....	....	....	....	2.0													
Group II (Liver Extract)																						
Case 9																						Fever and diarrhea 5th to 9th hospital day; later uneventful recovery; well 12 months later
Hemoglobin, Gm.		2.7	8.3	....	....	7.2	6.9	8.7	7.9	8.8	9.2	....	10.6	9.9	7.4	9.6	10.5	12.5	....	11.2	11.1	
Reticulocytes, %		....	....	2.5	....	2.5	3.1	8.9	9.1	2.6	2.7	....	9.9	10.4	11.2	12.1	10.2	8.2	....	7.3	8.5	
Therapy:																						
Transfusion, cc.		100*	100	100																		
Purified liver ext., units	I. M.	....	....	15	15	15	15	15	15	15	15	15	15	....	15	....	15	....	....	15		
Case 10																						High fever, diarrhea, abdominal distention, vomiting throughout hospital stay; staphylococcic septicemia developed in spite of sulfadiazine and penicillin; died 21st day; autopsy
Hemoglobin. Gm.		4.5	6.2	4.5	5.0	6.3	5.3	9.4	9.1	6.8	9.7	8.2	7.8	9.3	8.3	9.0	7.6	9.4	10.2	9.8	7.9	
Reticulocytes, %		....	0.5	0.5	0.5	0.5	2.2	0.5	1.0	1.3	0.2	3.0	2.2	1.2	....	1.0	1.9	1.5	1.2	4.1	1.0	
Therapy:																						
Transfusion, cc.		....	....	100	125	100	....	....	....	100	....	100	100	....	....	100	....	....	....	....	25	
Purified liver ext., units	I. M.	....	....	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	
Case 11																						Active scurvy; ascorbic acid, 100 mg. daily, since admission; no transfusion; no effect of folic acid; hemoglobin 10 Gm. on 27th day; well 4 months later
Hemoglobin, Gm.		6.6	....	5.9	....	5.4	5.3	5.9	6.5	6.7	8.5	....	6.3†	8.8	8.8	8.6	8.3	9.5	8.5	8.8	8.5	
Reticulocytes, %		....	....	2.1	....	3.9	6.2	15.4	21.4	18.2	7.4	....	3.3	4.7	2.5	3.0	1.7	3.0	2.5	1.9	1.0	
Therapy:																						
Purified liver ext., units	I. M.	....	....	15	15																	
Folic acid conc., mg.	Oral	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1.35	1.35	
Case 12																						Uneventful recovery; hemoglobin 11.2 Gm. 4 months later; well 6 months after discharge
Hemoglobin, Gm.		3.3	7.8	6.6	7.1	....	7.9	7.2	6.5	....	5.9	5.6	6.8	7.2	7.9	7.1	....	8.8	7.1	7.8	7.9	
Reticulocytes, %		1.7	....	1.1	2.5	....	1.6	2.3	1.0	....	1.8	2.4	12.1	11.3	8.6	8.6	....	8.2	7.7	7.5	6.8	
Therapy:																						
Transfusion, cc.		60	60																			
Purified liver ext., units	I. M.	....	....	....	....	....	....	....	15	15		....	....	....	15	....	....	15				

TABLE 3.—*Summary of Therapy—Continued*

	Administration	Days																			Comment
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Case 13	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Pneumonia; scurvy on admission (table begins 15 days later); had had 2 previous transfusions without lasting effect; chickenpox during otherwise uneventful recovery; well 2½ months later
Hemoglobin, Gm.		6.6	....	9.1	9.6	8.6	8.5	8.1	8.4	....	9.6	8.4	8.6	9.3	9.5	9.9	....	10.6	9.9	10.2	11.0	
Reticulocytes, %.		1.7	....	0.6	0.8	....	0.3	0.3	1.2	11.3	6.3	6.2	6.1	5.9	8.2	2.6	2.5	1.1	1.9	2.6	2.3	
Therapy:																						
Transfusion, cc.		80																				
Purified liver ext., units	I. M.	....	....	....	....	....	15	15														
Case 14	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Febrile; scurvy treated with 100 mg. ascorbic acid daily; pulmonary edema developed following parenteral fluid therapy; died; autopsy—decided marrow response
Hemoglobin, Gm.		5.1	....	....	3.9																	
Reticulocytes, %.		1.9	....	....	1.2																	
Therapy:																						
Transfusion, cc.		....	....	....	120																	
Purified liver ext.,units	I. M.	....	15	....	15																	
Case 15	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Uneventful recovery; no follow-up
Hemoglobin, Gm.		6.5	9.5	8.6	8.3	8.3	8.4	7.2	....	8.9	9.5	10.1	10.7	10.8	10.3	....	11.1	11.1	11.4	11.8	11.5	
Reticulocytes, %.		...	0.2	0.2	....	0.2	0.3	0.1	....	11.1	11.4	18.2	15.0	9.2	....	....	0.7	...	0.5	....	0.6	
Therapy:																						
Transfusion, cc.		130*																				
Crude liver ext., units...	I. M.	....	....	....	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4			
Case 16	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Uneventful recovery; well 2 months later
Hemoglobin, Gm.		5.1	4.2	6.3	6.0	....	6.7	....	....	8.2	....	....	....	8.0	....	8.8	....	10.2				
Reticulocytes, %.		0.1	....	....	0.8	....	2.1	....	....	5.3	....	....	....	....	....	2.9	....	1.6				
Therapy:																						
Transfusion. cc.		....	100	....	100																	
Crude liver ext., units...	I. M.	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4				
Case 17	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	High fever; intractable diarrhea; abdominal distention; coma; died; autopsy—mild enteritis, primary dural sinus, thrombosis
Hemoglobin, Gm.		4.2	4.4	7.4	6.6	5.5	8.1	7.6	9.0	11.1	11.3	13.1	12.6	12.0	....	11.8	13.1	12.6	12.5	11.6	12.0	
Reticulocytes, %.		....	4.8	5.4	....	3.2	1.2	....	....	3.6	2.3	1.3	2.5	1.4	....	....	3.0	6.1	7.6	4.9	8.6	
Therapy:																						
Transfusion. cc.		130*	130*	....	....	130	....	....	130	50												
Crude liver ext., units...	I. M.	....	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Case 18	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Admitted with severe icterus, fever and liquid stools; dehydration; died; autopsy—subacute hepatitis, mild enteritis
Hemoglobin, Gm.		5.3	5.5	5.5	7.4	6.5	7.4	....	....	6.5	8.8	8.1	7.8	8.0								
Reticulocytes, %.		....	0.0	0.0	0.3	4.8	2.4	....	....	0.0	....	7.9	2.6†	6.2								
Therapy:																						
Transfusion, cc.		50*	....	....	....	50*																
Crude liver ext., units...	I. M.	....	....	....	....	2	2	2	2	2	2	2	2	2								

Case 19	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Severe diarrhea, abdominal distention and fever developed during therapy with liver extract; later recovered uneventfully; well 1 month after discharge
Hemoglobin, Gm.		4.3	6.3	....	9.7	....	....	10.9	11.4	11.2	....	10.2	11.4	9.9	10.5	8.1	8.0	....	9.6	10.3	9.3		
Reticulocytes, %		2.3	2.2	....	0.5	....	....	0.6	0.2	0.3	....	1.2	3.2	1.0	4.2	2.8	3.8	....	1.4	1.3	1.4		
Therapy:																							
Transfusion, cc.		50	50	50																			
Crude liver ext., units	I. M.	....	....	....	....	....	....	....	....	....	2	2	2	2	2	....	2	2	....	2			
Group III (Transfusions Only)																							
Case 20	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Intractable diarrhea, bouts of fever; abdominal distention; development of icterus; died; autopsy—cholangiolitis, duodenitis and enteritis
Hemoglobin, Gm.		3.9	8.6	6.8	7.4	9.4	10.2	....	9.4	....	....	9.5	8.0	9.3	....	9.4	9.3	9.0	8.2	7.9	8.5		
Reticulocytes, %		1.4	....	1.2	....	....	0.5	....	2.3	....	....	1.4	1.0	0.8	....	0.6	0.5	0.2	1.0	0.5	0.6		
Therapy:																							
Transfusion, cc.		75*	....	....	50	50																	
Case 21	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Reported hemoglobin 6.2 Gm. before transfusion (500 cc.) at another hospital with massive subarachnoid hemorrhage 36 hr. after admission
Hemoglobin, Gm.		12.4																					
Reticulocytes, %		....																					
Therapy:																							
Transfusion, cc.		....																					
Case 22	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Ferrous sulfate given after discharge; uneventful recovery; last hemoglobin level 11.3 Gm. 1 mo. after discharge; no further follow-up
Hemoglobin, Gm.		5.1	....	6.1	....	8.1	8.8	8.0	8.3	8.0	8.4	....	....	....	....	....	....	....	9.2				
Reticulocytes, %		3.7	....	2.6	....	0.5	0.5	1.4	1.2	1.3	0.7	....	....	....	....	....	....	....	2.7				
Therapy:																							
Transfusion, cc.		75	90	....	....	....	....	....	....	....	100												
Case 23	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Salmonella typhimurium in stools; positive agglutination; fever 3 wk.; improvement in clinical and blood pictures coincide; no follow-up
Hemoglobin, Gm.		5.2	....	4.5	....	....	....	9.0	9.8	8.8	8.6	8.8	....	8.6	7.9	....	8.3	8.3	8.3	....	9.2		
Reticulocytes, %		1.1	....	3.5	....	....	....	0.1	0.1	0.1	0.1	0.2	....	0.1	2.2	....	2.7	1.7	5.5	....	5.9		
Therapy:																							
Transfusion, cc.		....	....	....	100	120	85																
Case 24	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Scurvy; ascorbic acid 300 mg. daily; uneventful recovery; well 4 wk. later
Hemoglobin, Gm.		5.4	4.7	6.8	8.2	8.6	9.1	....	9.8	10.4	10.9	10.6	10.6	10.4	....	10.7	11.1	11.5	....	11.2			
Reticulocytes, %		....	2.9	3.0	3.4	3.1	6.2	....	7.6	6.8	6.0	7.2	6.2	4.8	....	2.6	2.8	0.9	....	1.3			
Therapy:																							
Transfusion, cc.		....	200																				
Group IV (No Treatment)																							
Case 25	.....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Spontaneous remission in spite of fever for 1 wk.; hemoglobin 9.2 Gm.; reticulocytes, 10% 2 wk. later
Hemoglobin, Gm.		8.3	5.8	6.0	5.8	6.5	5.8	5.9	6.7	9.3	9.6	9.2	9.3	7.3	8.0	8.7	7.6	9.0	8.0				
Reticulocytes, %		....	7.1	7.0	7.4	6.2	....	7.1	11.9	12.4	15.1	17.1	11.4	11.6	9.1	5.8	3.4	2.8	3.8				

* Suspension of red cells in isotonic solution of sodium chloride.
† Possible technical error.

level and the red cell count continued to rise. The bone marrow underwent a striking transformation and assumed a normal pattern within a few days. Unless other illnesses interfered, the patient's appetite rapidly improved, the color returned and the irritability disappeared. Splenomegaly and hepatomegaly, when present, often persisted for weeks afterward but eventually also disappeared. During the follow-up period, ranging from three to twenty months, there were no recurrences of this type of anemia in any of the 17 patients who did not succumb to complications, although in some cases indications for iron or antiscorbutic therapy developed later.

During their hospital stay all patients, with 1 exception (case 5), received the usual diet according to age. Ascorbic acid and vitamin D were given to all but 2 patients from the start. Sulfadiazine was usually ordered because infection was suspected, if not actually proved. In some instances penicillin was given over a period of time.

Blood transfusions were deemed necessary for all but 2 patients because of the critically low levels of hemoglobin. In the latter part of the study, suspensions of red blood cells in isotonic solution of sodium chloride were used instead of whole blood. One patient had already received transfusions elsewhere before admission to our institution. To the first few patients, treated with liver extract, multiple transfusions were given, mainly because the hemoglobin level tended to fall in the presence of severe infection.

Later, the patients on admission received only enough blood or cell suspension to raise the hemoglobin to levels near 6 Gm. After a suitable period of observation, usually when the hemoglobin level had begun to fall again, and only if the reticulocyte count remained low, folic acid concentrate, synthetic folic acid or purified liver extract was administered. Liver extract was given in uniform doses of 15 units, while the amount of folic acid was varied in an effort to find a suitable dosage. No conclusions on this point were reached, but it was evident that in all cases adequate amounts had been given (table 3). For the purpose of establishing a minimum effective dose, this group was not suitable because of the serious general condition of many of the patients. In some cases transfusions had to be resorted to again later because of infections or because the fall of the hemoglobin level was so rapid that the response to specific treatment could not be waited for, but this did not necessarily interfere with the observation of reticulocyte responses.

An analysis of the results given in table 3 will be presented after a description of the bone marrow lesions and the results of examination of the blood.

Postmortem Observations.—It was evident that, like the clinical picture, the pathologic lesions were not uniform. A detailed summary of

the postmortem observations is given elsewhere.[3a] With the exception of 1 patient who died from pulmonary edema following a transfusion, the 7 deaths in this group were due to the serious conditions previously named. In most of the fatal cases multiple transfusions had restored the hemoglobin values to essentially normal levels, and the anemia, judged by the condition of the bone marrow and blood, was responding to specific treatment when such was given (table 3). A postmortem diagnosis of the type of anemia could not be made. This is at variance with opinions widely held by pathologists and requires discussion in a separate paper.

II. MORPHOLOGIC ASPECTS

Deficiency states affecting the bone marrow may produce anemia in at least two ways: Iron or other materials used in the synthesis of hemoglobin may not be available to otherwise normal cells, or the cells themselves may be abnormal because of a deficiency in an essential factor.

The outstanding example of the latter type of deficiency is pernicious anemia. In this condition the character of erythropoiesis in the marrow is profoundly altered, the regeneration of erythroblastic cells is disturbed and the normoblastic pattern changes to one characterized by dysplastic cells, generally referred to as megaloblasts.[4] The blood picture merely reflects this situation. Not only is the anemic state cured when the missing factor is supplied in adequate amount, but the marrow undergoes an almost immediate transformation from the megaloblastic to the normoblastic type.[5]

The correlation of structural patterns found in the bone marrow before and after therapy with the changes in the peripheral blood and with the clinical response of our 25 patients has convinced us of the existence of a similar dysplastic state occurring in infants, which has not yet received recognition. The morphologic pattern which characterizes this dysplasia is identical in its basic features with that seen in pernicious anemia and will therefore be referred to as megaloblastic.

Many writers, particularly in pediatric literature, have used the term "megaloblast" indiscriminately to designate any large nucleated hemo-

4. Jones, O. P.: Cytology of Pathologic Marrow Cells with Special Reference to Bone-Marrow Biopsies, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938.

5a. Rohr, K.: Das menschliche Knochenmark, Leipzig, Georg Thieme, 1940. (b) Koller, F.: Die Erythropoese bei der perniziösen Anämie mit besonderer Berücksichtigung der quantitativen Verhältnisse, Deutsches Arch. f. klin. Med. **184**:568, 1939. (*c*) Scott, R. B.: Sternal Puncture in the Diagnosis of Diseases of the Blood Forming Organs, Quart. J. Med. **8**:127, 1939. (*d*) Naegeli, O.: Ueber die Entstehung und Behandlung der Anämie, Wien. klin. Wchnschr. **48**:225, 1935. (*e*) Limarzi, L. R.: The Diagnostic Value of Sternal Marrow Aspiration, Illinois M. J. **75**:38, 1939. (*f*) Jones.[4]

globiniferous cell merely on the basis of size or level of maturation and have thus remained unaware of the existence of fine but distinct morphologic changes in the pattern of erythropoiesis which occur in certain anemias and must be looked for in order to be seen. The recognition of these changes, as Jones [6] has pointed out, is not an academic question to be left to cytologists but has direct clinical application. Failure to observe these aberrations means failure to distinguish between normal and dysplastic cells and until now has deprived the clinician of a basic tool in dealing with the anemias of infancy.

We are therefore in need of terms to express such distinctions and shall use the word "megaloblast" in a strict morphologic sense to designate pathologic marrow elements of the erythroid series corresponding to the cells described and illustrated under that name by Naegeli,[7] Rohr,[5a] Jones and others [8] and found mainly in addisonian anemia. A precedent for such usage in the pediatric literature has lately been set by Davis [9] with whose concept we are in essential agreement.

The cytologic details of megaloblasts, recognized by most hematologists and recently summarized by Jones,[6] are distinct only in smears and imprints of bone marrow. For this reason we have not resorted to the use of sections of fixed specimens. In adequately prepared smears, the nuclear structure in the earliest stages of development of megaloblasts shows a much finer and more evenly distributed network of chromatin than the normal cell at the corresponding stage. The parachromatin is abundant, often is acidophilic and equals or exceeds the amount of chromatin. There is little tendency to clump, and, when condensation of the chromatin occurs in later stages of development, the clumps are unevenly distributed and the parachromatin remains abundant and distinct, producing the characteristic "open" structure of the nucleus, which distinguishes it from the dense "spokewheel" or "checkerboard" nucleus of normoblasts. This persists even while the cytoplasm acquires its complement of hemoglobin and is often seen in completely acidophilic (orthochromatic) cells. A study of the entire series thus produces the impression of a lag between functional maturation (hemoglobinization) of the cytoplasm and that of the nucleus, with delay in nuclear condensation.[5a] Finally, megaloblasts are larger and have more cytoplasm than normal erythroblasts in corresponding stages of development,[5a] but size alone cannot be used as a criterion, since in pathologic condi-

6. Jones, O. P.: Morphologic, Physiologic, Chemical and Biologic Distinction of Megaloblasts, Arch. Path. **35**:752 (May) 1943.

7. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931.

8. Footnotes 4 and 6.

9. Davis, L. J.: Macrocytic Anemia in Children, Arch. Dis. Childhood **19**:147, 1944.

tions associated with hyperplasia of the bone marrow the size of the erythroblasts of normal nuclear pattern may also increase.[6]

Recognition of the megaloblastic type of erythropoiesis is essential because macrocytosis of the peripheral blood can be produced by several distinct cellular mechanisms [6] operating at the site of blood formation and, therefore, often recognizable only through a study of the bone marrow. Three of these mechanisms are of common occurrence and clinical significance. The first is an outpouring of reticulocytes, i. e. immature erythrocytes larger than mature cells, from normal marrow. The second is the presence of "macronormoblastic" marrow. Here the marrow is hyperplastic, the young basophilic forms are increased in number and the normoblasts are larger than those seen in normal marrow but retain otherwise normal structure. This mechanism operates in many unrelated conditions sometimes associated with a macrocytic anemia, for instance erythroblastosis fetalis, acute hemolytic anemia, hepatic disease, leukemia, aplastic anemia, congenital syphilis, Hodgkin's disease and many others.[6] This fundamentally normal type of erythropoiesis must be distinguished from the truly dysplastic type which constitutes the third fundamental cause of macrocytosis, i. e. megaloblastic erythropoiesis as judged by the criteria outlined.

It is evident, then, that anemias with a macrocytic blood picture are a heterogeneous group and that the study of cellular structure in the marrow and the knowledge of pathologic patterns make up an indispensable adjunct to the proper diagnosis, treatment and classification of these conditions. It is all the more important to realize this because mere occurrence of a reticulocyte response obtained in therapeutic tests with various antianemic substances cannot be considered sufficiently specific to distinguish anemias due to deficiencies of these factors from other macrocytic anemias. Reticulocyte crises of variable intensity may occur in response to nonspecific stimulation of the marrow by extracts of various organs, including liver,[10] and also may occur spontaneously in the course of many anemias. It is thus necessary in each case to apply certain rigid criteria in regard to the specificity of the reticulocyte response, and this will be done for our material.

Naegeli made the statement in regard to pernicious anemia that an even better criterion for the specific effect of therapy consists in the prompt transformation of megaloblastic into normoblastic marrow.[5d] With this statement we agree, though we modify it to include the transformation of dysplastic into normal marrow in conditions other than pernicious anemia.

10. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions, Lancet **2**:319, 1935. Naegeli.[5d]

A. The Changes in the Bone Marrow.—The qualitative changes in the bone marrow typical of our group of patients will be described first, because the altered state of the marrow organ which they express is responsible for the development of the anemia. The condition of the blood can then be understood as a reflection of the mode and degree of marrow function.

In the fully developed lesion of the marrow it was evident that both erythropoiesis and leukopoiesis were affected. A disturbance of thrombopoiesis could be inferred from the diminution of platelets in the blood and the scarcity of megakaryocytes in marrow smears. We were unable, however, to recognize significant qualitative changes in the megakaryocytes. Nonetheless, it was obvious that the marrow organ was affected as a whole, and the changes in the three systems seemed to parallel each other. In this respect, as in cytologic detail, the resemblance to pernicious anemia was striking.

Erythropoiesis: The disturbance in erythropoiesis was evident in the following features: prevalence of "young" basophilic and polychromatic cells; limitation of mitotic activity, mainly to the earliest stages of maturation; abnormal karyokinesis, with tripolar or multipolar mitoses and atypical chromosomes; an abnormal nuclear structure, which stamped these cells as megaloblasts in the restricted morphologic meaning of the term as defined previously; lobulation and distortion of the shape of the nuclei; an increased tendency to denucleation by karyorrhexis and sometimes by karyolysis, and an increase in the size of the cells and in the relative amount of cytoplasm at all levels of maturation.

These features were not always equally distinct, and minor variations were common. Somewhat atypical megaloblasts predominated in the cellular picture of some marrows, but, if the total pattern was considered rather than the structural details of a few individual cells, the picture was always unmistakable and could be easily identified by persons experienced in the study of bone marrow smears.

The changes in cellular structure are illustrated in figure 2. A more detailed description together with certain quantitative data on the bone marrow of these patients is given elsewhere.[11] At this point it is sufficient to say that the pattern which emerged from a study of these lesions corresponded basically to that seen in pernicious anemia in relapse. Such a pattern is typical of alterations produced by the lack of a so-called maturation factor.

Rohr [5a] has given an analysis of this marrow lesion which applies equally to pernicious anemia and to the megaloblastic anemia of infants described here. The mitotic activity of the erythropoietic elements is

11. Zuelzer, W. W.: The Pathology of Megaloblastic Anemias in Infants, to be published.

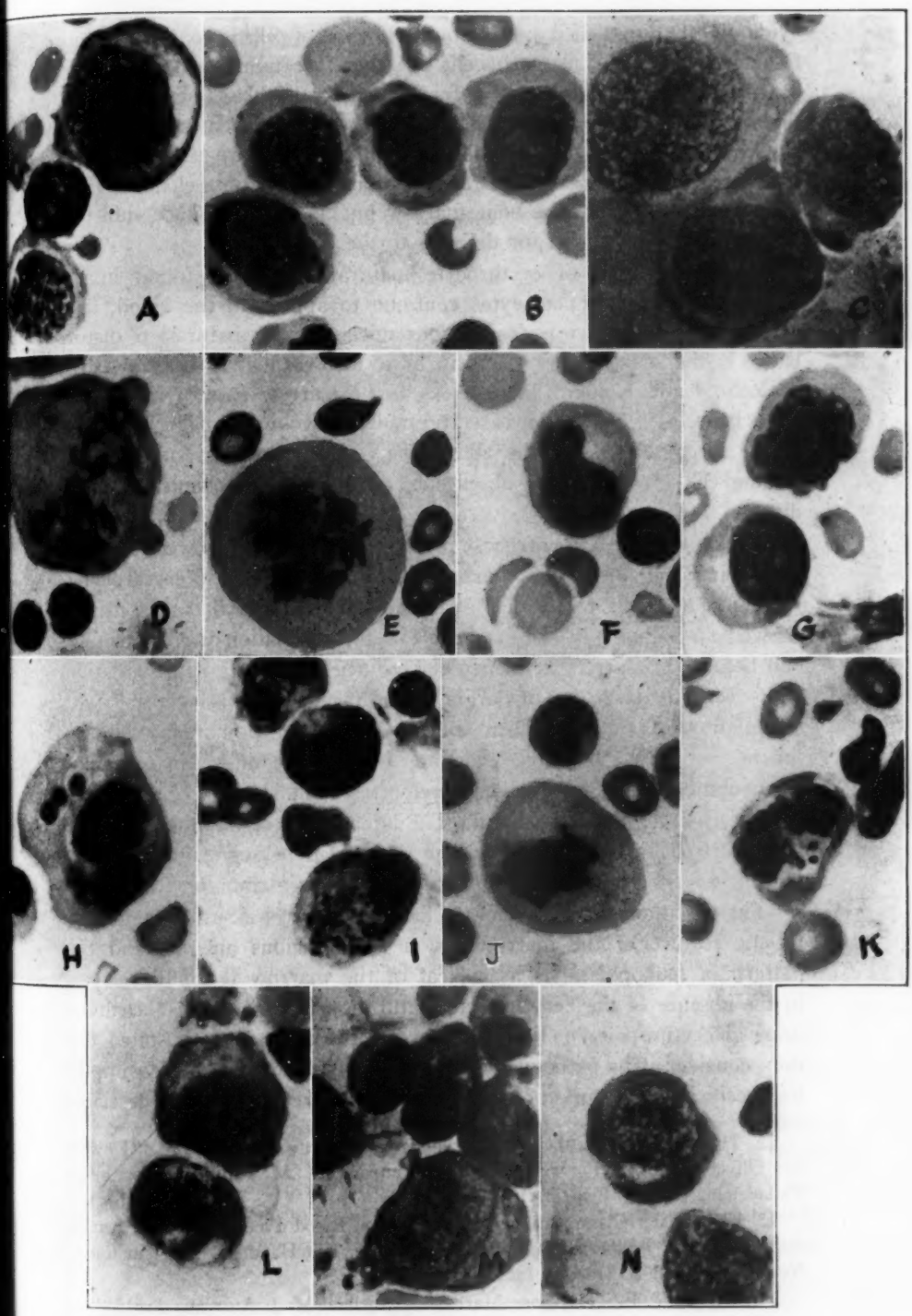

Fig. 2.—*A* through *C*, typical megaloblasts (cases 1 and 9); *D* and *E*, abnormal mitosis (case 9); *F* and *G*, nuclear lobulation and polychromatic megaloblasts, (cases 9 and 2); *H* through *K*, nuclear distortion and karyorrhexis, (cases 2 and 1); *L* through *N*, karyolysis in megaloblasts (cases 9 and 20).

evidently not diminished, but the multiplication of cells is confined mainly to primitive levels, and such cells are therefore numerous. The more sensitive because more highly differentiated erythroblasts near maturity, division of which ordinarily assures the rapid replacement of mature erythrocytes, have lost the ability to multiply and are therefore relatively scarce. The continued reproduction of immature elements may lead to hyperplasia of the bone marrow but does not produce sufficient numbers of erythrocytes for delivery to the blood.

Since all stages of erythrocyte maturation can be found in the marrow and since reticulocytes continue to appear in the blood, it is evident that the marrow lesion does not reflect a maturation disturbance in the strict sense of total inability to form mature cells. Rather, as Rohr [5a] and Koller [5b] have stressed, the marrow pattern indicates a disturbance of regeneration based on faulty karyokinesis. The large size of the megaloblasts and the abundance of the cytoplasm suggest continuing cell growth in the absence of an adequate mechanism for cell division.

Leukopoiesis: The precursors of the leukocytes showed constant qualitative changes no less characteristic than those of the erythrocytes. Here too, a "shift to the left" had taken place, and the cells usually showed an increase in size, but the exact classification was often difficult because of a strong tendency of the nuclei to undergo segmentation. Thus cells as large as or larger than normal promyelocytes [12] with granulation of the cytoplasm indicating decided immaturity showed indentation and lobulation, twisting, elongation and even beginning segmentation (fig. 3). Typical myelocytes with round, regular nuclei were, as a rule, virtually absent. The later stages of development were characterized by persistence of large size and hypersegmentation of the nuclei. Severe vacuolation of the cytoplasm was a common feature.

These pathologic granulocytes have been recognized as a characteristic feature of the marrow lesion in pernicious anemia, and this pattern of leukopoiesis is as typical of the marrow lesion developing in the absence of the "erythrocyte maturation factor" as are the alterations in erythropoiesis. Fallon [13] and T. E. Wilson [14] have stated that they consider it as pathognomonic, and Rohr's monograph also implies its specificity. To our knowledge it has not previously been described

12. The designation of the marrow cells is based on the nomenclature of Downey and Oliver P. Jones. For references see Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1944.

13. Fallon, M.: Classification of the Anemias, Blood Pictures in the Anemias, and Anemias of Infants and Children, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938.

14. Wilson, T. E.: The Bone Marrow in Anemia, M. J. Australia **1**:513, 1942.

in the marrow of infants. Jones,[15] in particular, has studied these "giant metamyelocytes" and "giant stab forms" and has stated that they are mainly pathologic promyelocytes with precocious polymorphism of the nucleus. Rohr [5a] has taken the stand, with which we agree, that these are indeed immature cells which, like the megaloblasts, lose the ability to divide in later stages of development and begin differentiation at an earlier stage than that of the myelocytes or metamyelocytes with which the process normally has its inception. The regeneration disturbance in granulopoiesis is thus comparable to that in erythropoiesis. Both

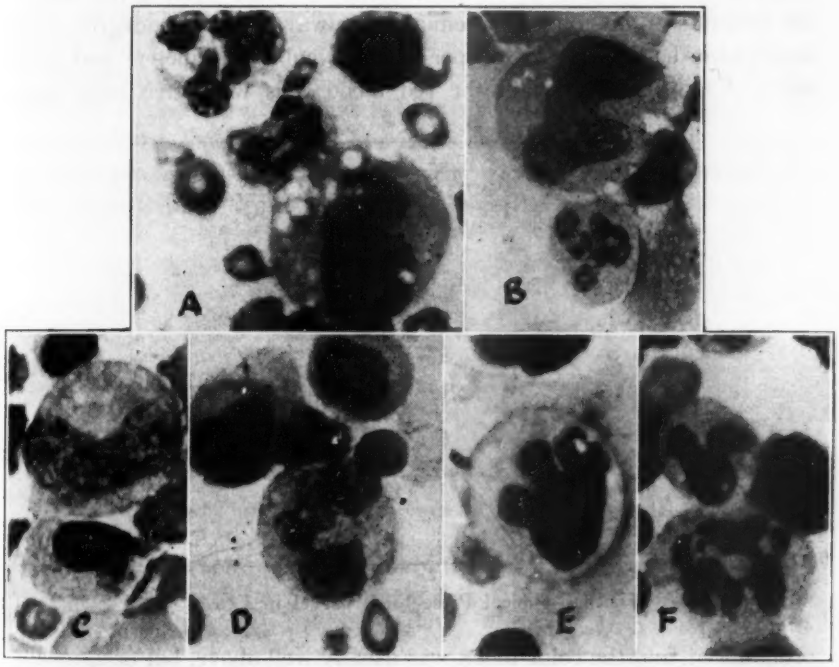

Fig. 3.—Typical abnormal granulocytes in the bone marrow in various stages of development.

lead to a decrease in the number of mature cells, i. e. to anemia and leukopenia, because of reduction in mitotic activity at the normally most active levels of multiplication.

Thrombopoiesis: Megakaryocytes were too rarely found in the marrow smears to permit the drawing of valid conclusions from their appearance. No striking alterations were noted, although Rohr [5a] has illustrated abnormal megakaryocytes in pernicious anemia. Occasionally we saw cells of this type with poorly developed azure granulation but

15. Jones, O. P.: Origin of Neutrophils in Pernicious Anemia (Cooke's Macropolycytes), Arch. Int. Med. **60**:1002 (Dec.) 1937.

well lobulated nuclei, suggesting a discrepancy between cytoplasmic maturation and nuclear differentiation similar to that seen in erythroid and granulocytic elements, but this was not a consistent finding. The presence of excessively large platelets in the blood and the thrombopenia did suggest, however, that the disturbance affected the megakaryocytes in the same manner as it did the erythroblasts and the precursors of the granulocytes.

B. The Changes in the Blood.—Erythrocytes: Table 2 gives the pertinent data on the blood of the 25 patients on admission. With the exception of case 21, in which transfusions had been given before the patient's admission, the anemia was always severe in degree, with hemoglobin levels near 5 Gm. per hundred cubic centimeters and often below 3 Gm. Reduction of the red blood cells was often even more

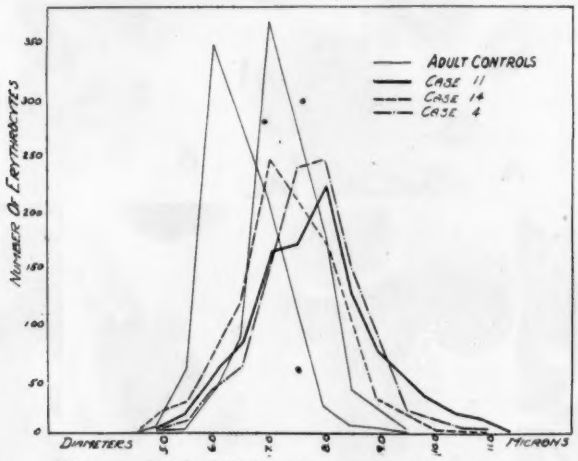

Fig. 4.—Typical Price-Jones curves in 3 cases.

pronounced, and the color index was usually well above, but occasionally below, unity. Study of the erythrocytes on smear often showed extreme anisocytosis, with numerous microcytes as well as excessively large macrocytes, so-called megalocytes. The variation in the diameters of the red cells is best shown in typical Price-Jones curves (fig. 4). The similarity of such curves to those obtained in pernicious anemia may be noted in passing.

The figures for mean corpuscular volume did not always indicate macrocytosis and in some instances were even below normal. This may have been due in part to inaccuracies inherent in the hematocrit method. As determined by this method, macrocytosis cannot be relied on for the hematologic diagnosis of this type of anemia, although it has been widely accepted as a basic criterion. Its absence does not eliminate the presence

of a megaloblastic anemia,[16] and, since an increase in mean corpuscular volume is observed in other conditions,[6] its value is limited.

The mature erythrocytes appeared well filled with hemoglobin, and this was borne out by the mean corpuscular hemoglobin concentrations. Polychromasia was not extreme, but a few deeply basophilic erythrocytes with hardly a trace of hemoglobin were found in every case. Punctate basophils were invariably present, although they had to be looked for in most cases. Howell-Jolly bodies and Cabot rings were often seen.

The percentage of reticulocytes was usually small, and the absolute numbers of such cells seldom was increased and obviously did not account for the macrocytosis of the blood.

Nucleated red cells were always found, but in some cases a prolonged search was necessary. Frequently the large size, the abundance of the cytoplasm, the leptochromatic character and the lobulation or distortion of the nucleus suggested that these cells were megaloblasts rather than normoblasts, and a tentative diagnosis could be based on these features.

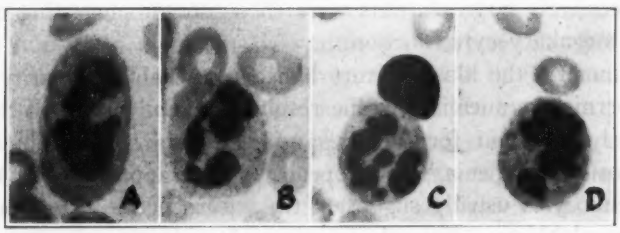

Fig. 5.—Neutrophil leukocytes in the circulating blood (cases 15, 13, and 11).

Generally these elements when found in the blood were too near maturity for their nature to be ascertained, and a study of the marrow was deemed necessary.

Leukocytes: The white cell count was below 10,000 per cubic millimeter in most cases, despite the presence of fever or other signs pointing to infection. In some cases a frank leukopenia existed or developed shortly after the patient's admission. Neutropenia was common, as a rule moderate but sometimes pronounced. No changes in the monocytes or lymphocytes were evident, but qualitative changes in the neutrophile leukocytes were sufficiently constant and characteristic to be of diagnostic importance. These cells were usually much larger than normal leukocytes. Two basic types were seen, with transitions between these extremes (fig. 5). The first was characterized by excessively large

16. Callender, S. T. E.: A Critical Review of Pernicious Anemia of Pregnancy, Quart. J. Med. **13**:75, 1944. Trowell, H. C.: The Morphology of the Blood in Dimorphic Anemia, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:151, 1942.

nuclei of the metamyelocyte type, often showing budding, twisting and beginning segmentation, while the granulation of the cytoplasm was uneven and suggested immaturity. These cells corresponded to the "giant metamyelocytes" and "giant stab forms" encountered regularly in the bone marrow. The second main type showed fully developed specific granulations of the cytoplasm and excessive segmentation of the nuclei, with long tenuous filaments connecting the lobules. Sometimes individual segments appeared isolated. These cells were also larger than normal and corresponded to the "macropolycytes" of pernicious anemia.

Strangely, the presence of these abnormal granulocytes seems to have been overlooked by students of the blood of infants. We have looked in vain for a single reference to this feature in the available literature. Yet in pernicious anemia it has long been recognized and rightly considered an important diagnostic feature.[17]

Platelets: The platelets were reduced in number, often decidedly so. The thrombopenia evidently accounted for the prolonged bleeding time and inadequate clot retraction in several cases and was considered the basis for the hemorrhagic manifestations in cases 8, 9, 10, 20 and 21. Often excessively large platelets were encountered, suggesting a disturbance in megakaryocyte function.

In summary, the blood picture had a remarkable similarity to that seen in pernicious anemia, but the results of examinations of the blood were rarely sufficient for the diagnosis, although the combination of macrocytosis, leukopenia, thrombopenia and the appearance of the neutrophil leukocytes usually suggested the nature of the condition. Only if true megaloblasts sufficiently immature for identification were found did examination of the blood establish the diagnosis, but this so rarely occurred that the demonstration of a megaloblastic bone marrow pattern was considered the only reliable single criterion.

III. ANALYSIS

To be meaningful, morphologic patterns such as we have described must correspond to physiologic patterns of response. The specificity of the marrow lesion can be assumed if a characteristic and consistent effect is produced by a specific therapy. Conversely morphologic changes occurring regularly under the influence of a given type of therapy tend to prove the specific action of the latter. This reciprocal relationship is axiomatic, not only in regard to megaloblastic anemias but in regard to other deficiency states, such as scurvy or rickets.

Two essential postulates must be fulfilled in order to demonstrate the specific nature of any form of antianemic therapy. The first is the occurrence of an orderly reticulocyte response within a definite period;

17. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1944.

the second is a consistent rise of hemoglobin and red blood count. Although these criteria were developed largely on the basis of studies on pernicious anemia, their general validity is obvious.

The factors to be considered in the interpretation of a reticulocyte response have been discussed in detail by Minot and Castle [10] and are well known to hematologists. The occurrence and the magnitude of such responses depend, among other factors, on the initial red cell count, and the reaction may be modified or prevented by the presence of infection, hepatic disease, nitrogen retention or the existence of other deficiencies affecting the bone marrow.

In our group of patients infections and other complications were common, and frequently multiple transfusions were necessary, which raised the red cell count beyond levels at which a characteristic reticulocyte response could be expected. These factors limited to 12 the number of cases suitable for evaluation of specific therapy by this means. In 2 additional instances, death occurred before a response was evident, from pulmonary edema developing in the patient during a too rapidly given transfusion in case 14 and from massive bilateral pneumonia in case 8. In a third case (case 7) a rise of the reticulocyte count to 5.9 per cent had taken place five days after the start of folic acid therapy, and the hemoglobin subsequently rose from 6.0 to 8.3 Gm., but the patient died from renal disease and acidosis within ten days.

In the 12 cases suitable for therapeutic studies (table 3), the effect of crude or purified liver extract given parenterally and that of folic acid appeared identical, whether the latter was given orally or parenterally in the form of concentrates or as synthetic material. A second reticulocyte response could not be produced by liver extract when folic acid had been given first and vice versa. Since liver contains folic acid, the identity of the therapeutic effect raises the question whether for this form of anemia liver extract is effective because of its folic acid content. Curves illustrating the typical sequence of events with both types of therapy are shown in figure 6.

The effects of folic acid and of liver extracts were as definite in regard to the leukocytes and platelets as in regard to the erythrocytes of the blood. The neutrophil leukocytes increased in number and the hypersegmented forms gave way to normal cells within seven to sixteen days. Sometimes a slight eosinophilia appeared. In several patients treated with relatively large amounts of synthetic folic acid, a transient leukocytosis with as many as 50,000 cells per cubic millimeter appeared simultaneously with the reticulocytosis. The platelets increased in number soon after therapy was started, and usually a sudden outpouring of these elements was observed on smears of the peripheral blood around the ninth day.

The criteria set forth in an earlier part of this paper enabled us to predict the effect of liver or folic acid therapy on the anemia in every case in which there were no complications by extraneous factors. This may be considered additional evidence for the specificity of both the marrow lesion and the therapy. For control purposes, folic acid concentrates and, in 1 instance, synthetic folic acid were used in 10 cases of

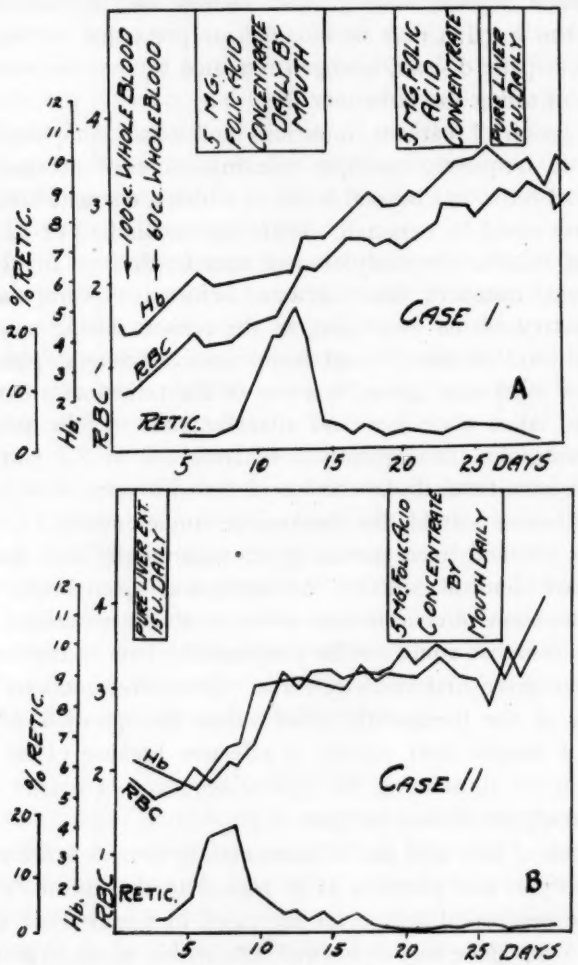

Fig. 6.—Response to oral administration of folic acid concentrate in case 1 and parenteral purified liver extract in case 11.

anemia of prematurity, in 1 case of hypochromic anemia, in 1 case of chronic hypoplastic anemia, in 1 case of aplastic anemia and in 1 case of sickle cell anemia. In none of these cases did folic acid seem to have any appreciable effect. The dosage of folic acid in this control group was only between 2 to 5 mg. per day, but since comparable amounts had

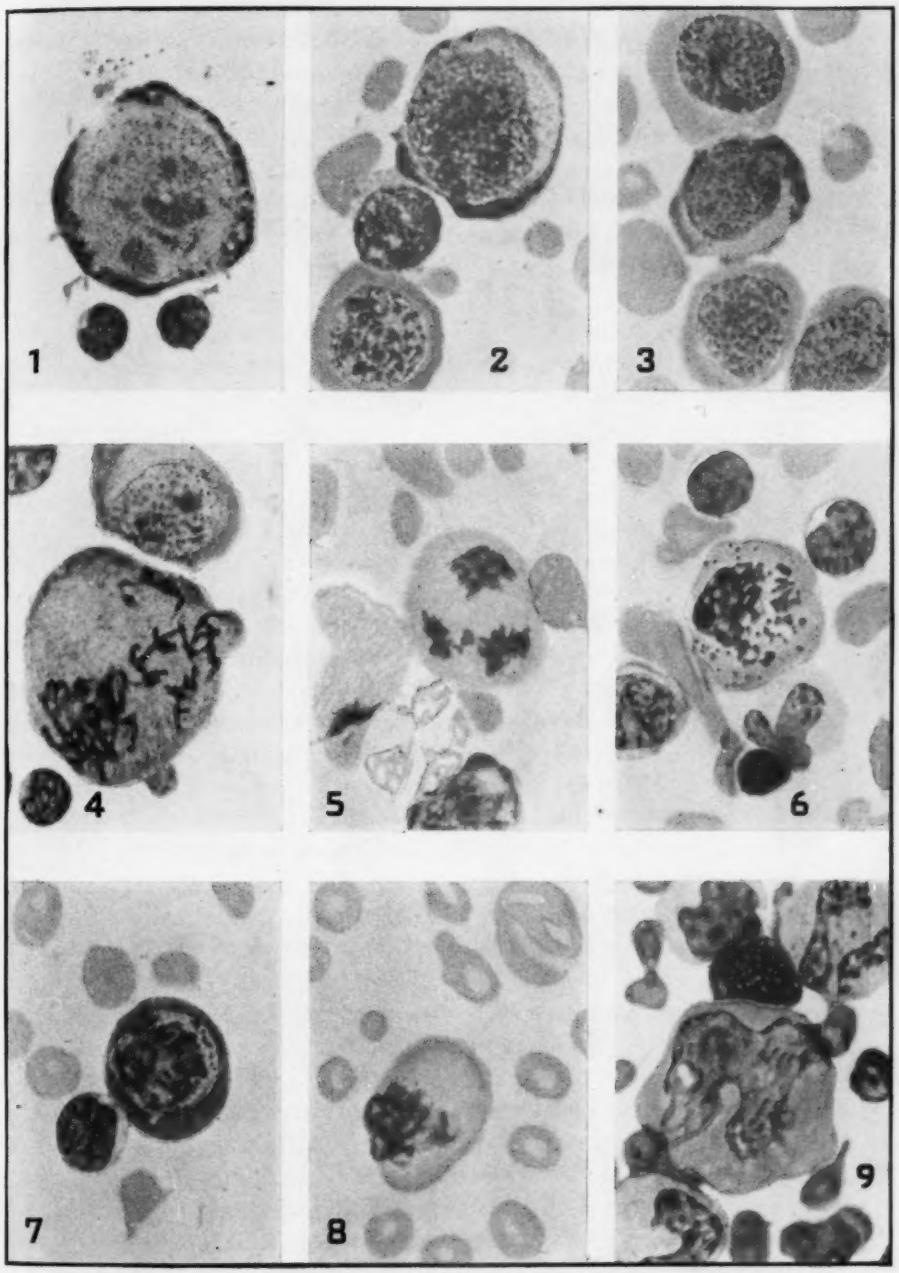

Fig. 7.—Photomicrographs made on Kodachrome film illustrating the typical pattern of bone marrow lesion in megaloblastic anemia (cases 1, 2, 9 and 20). *1, 2* and *3,* typical megaloblasts. *4* and *5,* pathologic mitosis. *6,* extreme karyorrhexis. *7,* beginning karyolysis. *8,* marked lobulation of nucleus in orthochromatic megaloblast. *9,* giant metamyelocyte.

proved adequate in the treatment of the megaloblastic type of anemia, it may be concluded that treatment in the control cases was ineffective. Further work along these lines is now in progress in our laboratory. It is possible that higher doses of folic acid may produce a favorable effect in types of anemia not related to a specific deficiency, just as liver can be effective in producing a reticulocyte response in anemias unrelated to a deficiency of hemopoietic principle, but, as in the latter case, such an effect would be nonspecific and would detract in no way from the significance of our observations.

The transformation of the pathologic into a normal marrow pattern in megaloblastic anemia is another indication of the specificity of antianemic therapy and was placed ahead of all other criteria by Naegeli.[5d] Prompt and complete transformation of the megaloblastic into a normoblastic pattern occurred in every one of the 22 patients treated with either liver extract or folic acid, whose marrow was restudied after therapy. This change was seen even when transfusions had interefered with the development of a reticulocyte response and thus it provided a means for judging the specific effect of therapy on these patients. In our earlier observations no effort was made to establish the time necessary to effect this transformation, and aspirations of marrow were not repeated until several weeks after the beginning of therapy. In the later part of the study, progressively earlier specimens were obtained after therapy. The earliest specimen, obtained two days after the first injection of folic acid, already showed complete disappearance of the megaloblastic pattern. The disturbance in granulopoiesis was as a rule still recognizable as late as a week after therapy was started but disappeared within two weeks to a month. The pronounced early hyperplasia of normoblastic elements, which accompanied the qualitative change in erythropoiesis in most instances, was suggestive but, as Naegeli stressed, not in itself evidence of a specific effect of therapy.

A few comments on the interpretation of our results are indicated. Since several patients had clinical scurvy, the possible effect of ascorbic acid had to be eliminated. This was possible directly in case 5 (fig. 6 *B*) in which antiscorbutic therapy was withheld until the reticulocyte response to folic acid had taken place. In the other 11 cases in groups I and II, ascorbic acid was given as a routine procedure from the first hospital day. Since it failed to produce either a characteristic reticulocyte response or a change in the marrow pattern and, on the other hand, these effects were clearly related in time to administration of liver and of folic acid a specific influence of antiscorbutic therapy on this type of anemia can be excluded.[18]

18. Davis, L. J., and Davidson, L. S. P.: Proteolyzed Liver in the Treatment of Refractory Anemias, Quart. J. Med. **13**:53, 1944.

In 2 of our patients who also received ascorbic acid (cases 22 and 24) transfusions were followed by lasting improvement of the blood picture though not by characteristic reticulosis. Similar observations were made by Cooley and Lee [19] on patients with a so-called pernicious picture of infancy, which was probably identical with the anemia described here. Since most of the patients who were later treated specifically had first received one or more blood transfusions as an emergency measure on admission, the possible effects of transfusion require comment. They are subject to several interpretations. The patients might have been on the verge of a spontaneous remission at the time the transfusions were given. Such remissions occur in addisonian pernicious anemia [10] and were illustrated in our material by case 25, in which the marrow and blood picture changed without any form of therapy. Second, the nonspecific influence of the transfusions on an existing infection might have enabled the marrow cells to utilize the hemopoietic principle already stored in the body. Third, transfusion with whole blood might have introduced into the organism specific substances contained in the plasma in amounts adequate to overcome the deficiency. In an attempt to eliminate this possibility, several patients received transfusions of thrice washed red blood cells suspended in isotonic solution of sodium chloride. In these patients reticulocytosis did not occur without further specific therapy, nor was the elevation of the red cell count following such transfusions of lasting character. These observations strongly suggest that the third possibility regarding the effect of whole blood transfusions is the correct one. In 1 patient it was possible to observe the effect of specific treatment without preceding transfusion (fig. 6*A*).

Vitamin B preparations were given to many of the first patients studied by us without producing a noticeable effect. In the patients treated with folic acid, such supplementary therapy was not used and therefore need not be considered in this context.

Misinterpretation of results was guarded against in the cases in which liver extract or folic acid was used by watching the reticulocyte count before the start of such therapy. The occurrence of a spontaneous remission (in case 25) has already been mentioned and was the reason for withholding therapy in this case.

IV. ETIOLOGIC FACTORS

In the preceding section the morphologic alterations of the bone marrow were described, and the effects of folic acid and of liver extracts were analyzed. If the conclusions concerning the specificity of both phenomena are correct, we may define the condition clinically as an

19. Cooley T. B., and Lee, P.: Pernicious Blood Pictures in Infancy, J. Pediat. **1**:184, 1930.

anemia of infancy characterized by a megaloblastic dysplasia of the bone marrow which responds specifically to folic acid or liver therapy and physiologically as a deficiency state of the marrow organ in regard to an essential hemopoietic factor contained in synthetic folic acid and commercial liver extracts.

The anemia may be explained, in analogy to the pathogenesis of pernicious anemia, as the result of a disturbance in the regeneration of marrow cells which limits the production of mature erythrocytes, leukocytes and platelets. It remains to examine the evidence regarding etiologic factors responsible for the development of the deficiency state.

The age and race of the patients appear significant. During the sixteen month period of study, only 1 comparable case of anemia in an older child was seen. The patient was a 5 year old girl with celiac disease, whose anemia promptly responded to liver extract. In our experience megaloblastic anemia in children beyond infancy is extremely rare, and this is confirmed by a study of the literature recently summarized by Davis.[9] Thus it may be said that in infants there is a greater tendency toward the development of a megaloblastic anemia than in children, just as hypochromic anemia is more common at this age.

It was striking that not one of the 25 patients was of Negro stock, although Negroes constitute between 30 and 35 per cent of all patients admitted to this hospital. This recalls the low incidence of addisonian pernicious anemia in adult Negroes.[20]

With only 1 exception the social-economic level of the parents was average for this community or better. Generally, the children had been cared for in adequate surroundings; none could be described as neglected. One patient (case 18) had been at another hospital from birth until she was transferred.

Prematurity per se did not seem to be a factor. Only 4 of the 25 patients were born prematurely, but it is noteworthy that of the 4 patients under 3 months of age 3 were premature twins. This would suggest that in cases in which the anemia developed in the first trimester prematurity was a contributing factor.

In 6 of the 23 mothers in the group on whom blood studies were done, anemia existed at the time when the patients were seen or had existed during pregnancy. The type of anemia in the mothers could not always be ascertained because of treatment received prior to examination. In 1 instance the mother's hospital record showed a hemoglobin level of 6.9 Gm. shortly after delivery (case 15), but the baby was given out for adoption and no further information could be obtained. Another mother (case 18) had hypochromic anemia, but she had suffered a severe post-

20. Murphy, W. P.: Anemia in Practice, Philadelphia, W. B. Saunders Company, 1939. Wintrobe.[17]

TABLE 4.—*Summary of Dietary Histories*

Case	Age, Mo.	Type of Feeding	Cereals	Vegetables	Meat	Eggs	Vitamin C	Vitamin D	Vitamin B	Appetite Before Present Illness
1	12	Whole cow's milk	Since 5 mo.	Since 6 mo.	—	—	Since 1 mo.	Since 1 mo.	Iron preparation	Good
2	12	Whole cow's milk	Since 6 mo., poorly taken	Since 9 mo., poorly taken	Broth	Custard	+	+	Multivitamin preparation since 9 mo.	—
3	4	"Similac"—evaporated milk	+	Since 3 mo.	—	—	+	+	—	Good
4	9	"Similac"	—	—	—	—	Since 3 mo.	Since 3 mo.	—	Good
5	9	"Similac"	—	—	—	—	—	—	Multivitamin preparation for 3 mo.	Poor—3 mo.
6	9	"Similac"	Since 7 mo.	Since 7 mo.	Liver soup	Custard	—	On and off	—	?
7	2	Evaporated milk	—	—	—	—	+	+	—	Good
8	4	"Similac"	Since 3½ mo.	—	—	—	Since 1 mo.	Since 1 mo.	Multivitamin preparation since 1 mo.	?
9	11	Breast	—	—	—	—	Until 8 mo.	Until 8 mo.	—	Good
10	8	"SMA"	+	+	—	+	+	+	—	Good
11	11	Homogenized milk	+	+	?	?	Irregular small amounts	—	—	Good
12	3	Whole cow's milk	—	—	—	—	—	+	—	Good
13	11	Evaporated milk—"SMA	Since 9½ mo.	Since 9½ mo.	—	—	—	—	—	Poor—4 mo.
14	9	"Similac"	Since 4 mo.	—	—	—	Since 4 mo.	Since 4 mo.	—	Good
15	5	Evaporated milk	+	—	—	—	+	+	Brewers' yeast	Good
16	16	Goat's milk	Until 12 mo.	Until 12 mo.	—	—	+	+	—	Poor—4 mo.
17	4	Homogenized milk	+	—	—	—	+	+	—	Regular
18	2	Evaporated milk	—	—	—	—	?	?	Iron and copper preparation	Gavage
19	3½	"SMA"—evaporated milk	—	—	—	—	Since 10 wk.	Since 10 wk.	—	Good
20	2½	"SMA"	—	—	—	—	—	—	—	Good
21	13	Breast	—	—	—	—	Until 11 mo.	Until 11 mo.	—	Poor—2 wk.
22	8	"Similac"	—	—	—	—	Poorly taken	Until 4 mo.	"Vi-Penta" for 3 mo.	Poor
23	7	Whole cow's milk	Since 6½ mo.	Since 6½ mo.	—	—	Not taken	+	—	Good
24	8	Evaporated milk	—	—	—	—	—	—	—	Poor—2½ mo.
25	9	"Similac"	—	—	—	—	Until 8¾ mo.	+	—	Fair

partum hemorrhage, and the significance of the hemoglobin level of 8.8 Gm. two months later was doubtful. A mild normochromic anemia was encountered in the mother of the twins (cases 19 and 20). The mother of one infant (case 12) had a moderate anemia, for which she was being treated with liver extract.

Cases 9 and 21 are particularly interesting because of the fact that both infants had received only breast milk for approximately a year. The mother of the first had a severe hypochromic anemia with glossitis and achlorhydria which later responded to therapy with iron preparations and the maternal grandmother had received treatment for pernicious anemia for a number of years. In the other case the mother was said to have pernicious anemia. She had received injections of liver extract on and off for eight years, and when her blood was examined by us no evidence of anemia was found.

With the exception of the identical twins (cases 19 and 20), none of the patients' siblings had, or gave a history of, a similar anemia. One patient was the fifteenth child in the family, and a sibling born subsequently had shown no anemia up to the age of 4 months.

The incidence of maternal anemia seems rather high, but the group is too small for statistical conclusions. No inference should be drawn from the fact that several of the mothers were being treated with liver extract, because of the indiscriminate use of this therapy in current practice.

Information concerning transfer of hemopoietic principle in breast milk of normal women was not available, but the occurrence of the anemia in 2 infants whose diet had consisted only of breast milk and whose mothers both had conditions associated with achlorhydria suggested a deficiency in the composition of the breast milk, and the anemia in these cases was interpreted as the result of a nutritional deficiency.

This leads to a consideration of the diets received by these patients. (table 4) In case 16 the child had taken nothing but goat's milk for the last four months.[20a] The studies of European investigators [21] on so-called goat's milk anemia leave little doubt that a diet of goat's milk frequently leads to the development of a macrocytic anemia, and the megaloblastic character of the marrow in such cases has led Rohr to

20a. Among the 4 additional cases referred to in an earlier footnote, was another infant whose diet had consisted solely of goat's milk and whose anemia promptly subsided on treatment with synthetic folic acid without changing the diet.

21. Glanzmann, E.: Klinische und experimentelle Studien über Ziegenmilchanämie und Dystrophie, Jahrb. f. Kinderh. **111**:127, 1926. György, P.: Beitrag zur Pathogenese der Ziegenmilchanämie, Ztschr. f. Kinderh. **56**:1, 1934.

include goat's milk anemia in the group of symptomatic pernicious anemias.[5a]

Thus, in 3 of the cases a causal relationship between a nutritional deficiency due to inadequate diet and the development of the anemia seems definite.

In the remaining 22 cases such a relationship is less easily demonstrated. The infants had been given artificial formulas, consisting of dilutions of standard commercial brands of evaporated or dried cow's milk in 17 instances and of fresh pasteurized milk in the remainder. The composition of the formulas was always satisfactory, and the amounts adequate, although not all patients ate well.

For 5 of the older infants the nutritional history was excellent, and a dietary deficiency may be excluded from the etiologic factors. Of 18 other patients who had not been given supplementary foods such as cereals, vegetables, meats or eggs, 7 were under 6 months of age and by current standards cannot be considered to have received inadequate diets. This leaves 11 patients out of 22 whose diet had been distinctly below average.

In 11 cases orange juice or ascorbic acid preparations had not been given. Five of these patients and a sixth, who had received a "multivitamin" preparation, had clinical evidence of scurvy. Vitamin D, cod liver oil or similar preparations were lacking in the diet of 7 patients, but rickets was not encountered in the entire group.

The 20 per cent incidence of scurvy appears too high to be merely incidental, but it must be remembered that the majority of the patients had received adequate amounts of ascorbic acid and showed no signs of scurvy. Moreover, megaloblastic anemia was not encountered in the vast majority of infants with scurvy studied in our clinic. The incidence of scurvy may be taken as a general index of the frequency of dietary inadequacies among our patients and not as an indication of an etiologic relationship between vitamin C deficiency and megaloblastic anemia, nor does a simple cause and effect relation between the diet and the anemia seem likely.

As important as the quality and amount of food offered is the manner in which it is taken, retained and digested. Most of the patients had shown a good appetite until a few weeks or days before admission. Vomiting was a common complaint, usually of only a few weeks' duration, although in some cases it had begun shortly after birth (table 1). The duration and severity of this symptom rarely seemed sufficient to explain the development of a deficiency state through loss of essential dietary factors by this mechanism, especially since pallor often was noted

at the time when vomiting first occurred. Similar considerations apply to the possible role of diarrhea, which usually preceded admission by several days or, at most, weeks.

In this group no chronic conditions interfering with absorption of food substances, such as malformations of the gastrointestinal tract, celiac disease or chronic gastroenteritis, were represented. The occasional association of macrocytic anemia with such states has been reported,[22] and the fact that the anemia in these cases responded to liver extracts makes it likely that it was of the megaloblastic type reported here.

While it appears that in infants a deficiency in regard to the hemopoietic principle found in folic acid can be produced by an inadequate diet and probably by conditions interfering with proper absorption in the intestinal tract, it seems doubtful that these are the only factors concerned in the production of the syndrome. We were impressed with the frequency of infections in our patients. In 21 cases cough and coryza had been present for several weeks or months, and most of the infants had fever. Pallor usually followed shortly in the wake of such symptoms. In 1 case a Salmonella infection was demonstrated, but infections of the respiratory tract predominated. These were of no unusual severity, and it was unlikely that they alone were responsible for the development of this type of anemia. The influence of constitutional predisposition is suggested by the age and racial background of the patients. If infections did play a part in the causation, as we are inclined to believe, it remains to be seen whether their action interferes with the assimilation, absorption or utilization of the hemopoietic principle. The demonstration of histamine-refractory achlorhydria in 9 of the 10 patients on whom gastric analyses were performed suggests a disturbance in assimilation (table 1). Yet achlorhydria in infants must be interpreted with a great deal of caution.[23] The results of gastric analyses in our patients repeated after the anemia was cured are not yet available. Further work along these lines is needed, but the solution of many of these problems seems to lie in the application of chemical or bioassay methods for the folic acid content of body fluids and tissues in normal infants and in patients with megaloblastic anemia.

The possible role of sulfonamide compounds must be mentioned, since anemia and agranulocytosis have been reported following the use

22. Goldhammer, S. M.: Macrocytic Anemia in Cancer of the Stomach, Am. J. M. Sc. **195**:17, 1938. Hardwick, C.: Prognosis in Coeliac Disease, Arch. Dis. Childhood **14**:279, 1939. Oppenheim, A.: Abels, J. C.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract, J. A. M. A. **127**:273 (Feb. 3) 1945.

23. Wolman, I. J.: Gastric Digestive Secretions in Infancy and Childhood, Am. J. M. Sc. **206**:770, 1943.

of these drugs,[24] possibly because these drugs interfere with bacterial synthesis of folic acid in the intestinal tract. Only 7 of our patients had received sulfadiazine before admission, sometimes repeatedly, but always in customary therapeutic doses and not for more than a few days at a time. In no case had a reaction been noted. We have no evidence that sulfonamide compounds were a causative factor in the development of the anemia in any of our patients. Nearly all patients were given sulfadiazine during their hospital stay. There was no evidence that it interfered with the effects of liver extract or of folic acid given orally or parenterally.

Since recovery appeared to be permanent and sometimes was observed even without specific treatment, it is clear that megaloblastic anemia of infants is not the same disease as addisonian pernicious anemia, although the nature of the marrow disturbance in the two conditions is similar if not identical. Failure to appreciate this has been due to the similarity in the blood picture and occasionally even in the pathologic observations and seems to have been responsible for the occasional reports of "true" pernicious anemia in infants found in the literature.[25]

SUMMARY

Twenty-five infants with a macrocytic anemia were studied. Evidence is presented to show that a characteristic dysplasia of the marrow encountered in these patients and the specific response to a hemopoietic factor contained in liver extract, folic acid concentrates and pure folic acid constitute criteria for the recognition of a distinct syndrome of common occurrence in white infants. The designation "megaloblastic anemia" is suggested for this condition because macrocytosis as determined by mean corpuscular constants is an inadequate criterion in the hematologic diagnosis of this anemia, while megaloblastic transformation of the bone marrow is a constant occurrence. The characteristics of the circulating blood are a normochromic and usually macrocytic anemia, leukopenia, neutropenia and thrombopenia, and they have a striking similarity to those of classic addisonian pernicious anemia. However, these charac-

24. Layne, J. A., and Schemm, M. D.: Acute Macrocytic Hemolytic Anemia Occurring Following Administration of Sulfadiazine, J. Lab. & Clin. Med. **29**:347, 1944. Vilter, C. F., and Blankenhorn, M. A.: The Toxic Reactions of the Newer Sulfonamides, J. A. M. A. **126**:691 (Nov. 11) 1944.

25. Sorochowitsch: Ueber einen Fall von tötlicher Kinderanämie (perniciöse Anämie?) mit Erythropoese und myeloider Umwandlung der Milz und Lymphdrüsen, Inaug. Dissert., Zurich, A. Markwalder, 1904. Starck: Die basophile Granulation (Punktierung) der roten Blutkörperchen im embryonalen Blute und bei anämischen Zuständen im Kindesalter, Jahrb. f. Kinderh. **69**:264, 1909. Koch, G.: Ueber perniziöse Anämie und extramedullare Blutbildung im Säuglingsalter, ibid. **71**:140, 1910. Langmead, F. S., and Doniach, J.: Pernicious Anemia in an Infant, Lancet **1**:1048, 1937.

teristics of the circulating blood are not constant, but study of the bone marrow by means of smears is a reliable method of diagnosis and can be easily and safely done.

The pathogenesis of the syndrome is discussed, and the anemia, leukopenia and thrombopenia are interpreted as the results of a disturbance of regeneration affecting the marrow cells and identical in its mechanism with the disturbance of marrow function in pernicious anemia.

Folic acid is identical with or contains a hemopoietic factor which has a specific effect on megaloblastic anemia. This effect is indistinguishable from that produced by purified commercial liver extract. Megaloblastic anemia of infants is defined as a deficiency state in regard to the factor—or factors—contained in these substances. In contrast to pernicious anemia, the deficiency is not a permanent one.

In an analysis of etiologic conditions, infections and nutritional deficiencies appear significant, while age, race and possibly prematurity and maternal anemia are predisposing factors.

Dr. Oliver P. Jones, of the University of Buffalo, and Dr. Lawrence E. Berman, of Wayne University College of Medicine, reviewed much of the material presented in this study and made stimulating comments; Dr. James L. Wilson, of the University of Michigan, criticized the manuscript; Dr. Icie G. Macy and her staff helped in the preparation of the manuscript, and Mr. Charles Zinser helped with the technical problems. The visiting staff of Children's Hospital gave permission to study some of their patients, and the resident staff cooperated in the study.

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EFFECT OF WAR-IMPOSED DIETARY LIMITATIONS ON GROWTH OF PARIS SCHOOL CHILDREN

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THIS paper represents data concerning comparative heights and weights of Paris school children, as recorded by school doctors and nurses, before and after the five years of restricted dietary intake incident to the war.

The survey of the records of 2,595 children, of whom 1,299 were boys and 1,296 were girls, was carried out in the following way: The

Weight and Height Averages of Paris School Children of Different Ages, in 1938 and 1944

Age, Years	Number	Weight, Pounds			Height, Inches		
		In 1938	In 1944	Difference	In 1938	In 1944	Difference
				Boys			
6	17	47.9	40.6	—7.3	45.7	43.2	—2.5
7	242	48.4	47.8	—0.6	46.2	45.5	—0.7
8	37	56.5	52.4	—4.1	49.4	47.6	—1.8
9	243	59.3	56.3	—3.0	49.4	49.2	—0.2
10	47	66.0	62.7	—3.3	52.5	52.2	—0.3
11	262	71.4	68.0	—3.4	56.2	53.1	—3.1
12	44	83.2	75.3	—7.9	56.7	55.2	—1.5
13	212	85.5	81.4	—4.1	57.6	55.6	—2.0
14	26	101.5	90.1	—11.4	61.3	59.7	—1.6
15	139	113.0	105.3	—7.7	63.2	62.4	—0.8
16	30	135.5	125.9	—9.6	66.1	65.5	—0.6
				Girls			
6	14	43.6	41.7	—1.9	44.0	43.3	—0.7
7	234	46.9	45.5	—1.4	44.8	43.3	—1.5
8	35	55.4	52.1	—3.3	48.3	46.9	—1.4
9	237	56.1	53.4	—2.7	49.0	47.8	—1.2
10	44	69.9	62.8	—7.1	53.3	52.0	—1.3
11	260	72.2	69.3	—2.9	54.1	53.5	—0.6
12	41	86.7	79.2	—7.5	57.8	56.3	—1.5
13	223	90.6	87.6	—3.0	58.3	57.8	—0.5
14	39	103.7	101.4	—2.3	60.6	59.5	—1.1
15	134	106.5	104.1	—2.4	61.3	60.3	—1.0
16	30	120.2	124.5	+4.3	62.2	63.0	+0.8

heights and weights of children from 6 to 16 years of age were taken at random in a certain number of schools in 1938 and 1944. The

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averages for 1938 and 1944 for each year of age were then determined, as given in the accompanying table and plotted on charts 1 and 2. The smooth lines on the charts indicate the weights and heights per year of age below which 10, 25, 75 and 90 per cent of children in the United States will fall on the basis of the statistical average, and thus provide

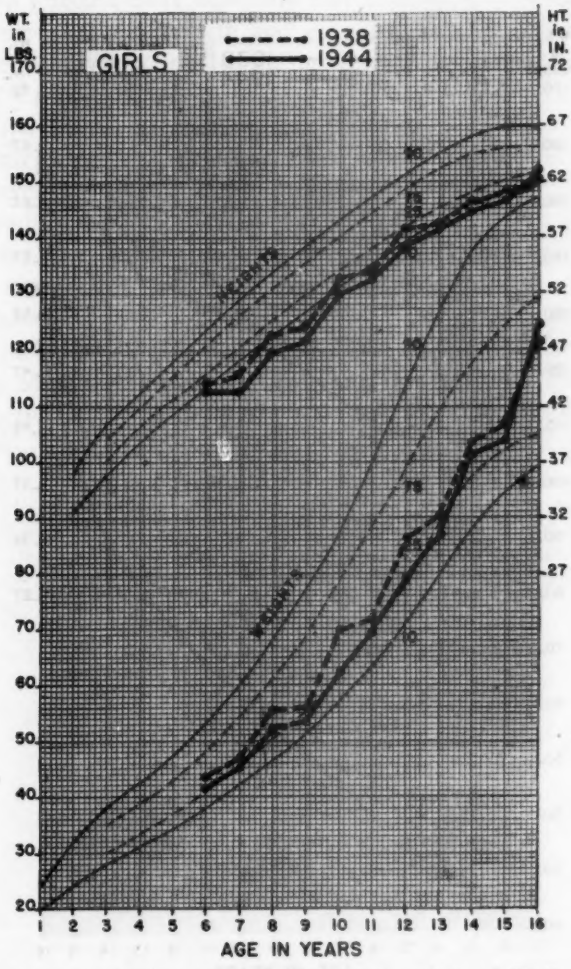

Chart 1.—Curves showing average height and weight of Paris school girls in 1938 compared with the average height and weight of school girls of the same age in 1944.

a standard against which the Paris children may be appraised. In general, the average weight and height of Paris children of the same age is less in 1944 than in 1938.

Among the boys the average deficit in weight in 1944 as compared with 1938 is 6 pounds (2.7 Kg.). The difference is more pronounced

for the adolescents of 12 to 16 years than for the younger boys, the maximum difference of 11.4 pounds (5.2 Kg.) being at 14 years. In the case of girls, the deficit in weight is not so great, the average being 3½ pounds (1.5 Kg.). The difference for the years from 10 to 13 was somewhat greater than for other ages. In contrast to the lesser

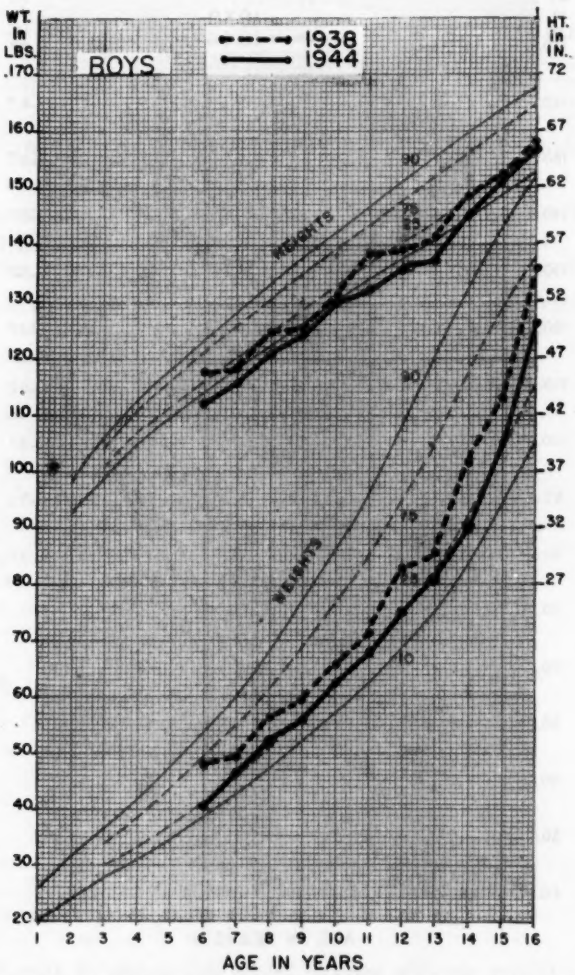

Chart 2.—Curves showing average height and weight of Paris school boys in 1938 compared with the average height and weight of school boys of the same age in 1944.

average weight in 1944 for ages 6 to 15, the average weight of girls 16 years of age was greater in 1944 than in 1938. This paradox can be explained by the fact that most of the older girls worked on farms during their vacations and thus obtained the benefit of better food.

Similarly, the average height was less for all age groups of both boys and girls in 1944 than in 1938, except for girls of 16 years. The maximum difference was for boys, 3.1 inches (7.7 cm.) and for girls, 1.5 inches (3.8 cm.).

The suggestion provided by these data that the adolescent growth of boys was affected more adversely than that of girls is supported by a recent survey of the growth and development of children suffering three years of inadequate diet during internment in Japanese prison camps.[1]

From the curves of charts 1 and 2, it would appear that Paris children under the normal conditions of 1938 were on the average slightly below the average height of children in the United States. The retardation in growth incident to the dietary conditions prevailing in 1939 and 1940 appears to have affected height and weight in relatively the same order of magnitude.

The apparent response of girls of 16 to better diet would appear to justify optimism as regards the ability of the majority of these children to respond to a normal dietary intake. However, the increased incidence of active tuberculosis during the war years prescribes a speedy reinstitution of adequate diets if the effects of such infection are to be arrested.

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1. Butler, A. M.; Ruffin, J. M.; Sniffen, M. M., and Nickerson, M. E.: The Nutritional Deficiencies Suffered by Civilians During Internment in Japanese Prison Camps in the Philippines and Recovery Therefrom, New England J. Med. **233**:639, 1945.

EFFECT OF GROWTH AND DEVELOPMENT ON ABNORMAL LABIAL FRENUM

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What the gods dared not promise to thy prayers,
time, as it rolls on, has bestowed.—VIRGIL.

THE rapid pace of growth and development in childhood impels a natural rehabilitation in the course of which many functional and structural deviations from the normal are corrected. Familiar examples will come to every pediatrician's mind—the molding of irregular head contours, the straightening of angular deformities of long bones disproportioned through scurvy or osteomyelitis, the filling out of thoracic defects, the alinement of alveolar margins temporarily distorted by thumbsucking and the retractions of umbilical protrusions. More dramatic even than these is the multitude of abnormal functional disturbances which are outgrown, spectacular examples of which were presented by Dr. Holt[1] in his last public address, given at Peking Union Medical College in 1923. These changes, Dr. Holt stated, are not as curious as they may seem to be, when it is recalled that four times during the period of pediatric observation the child doubles its weight: at 6 months, by the end of the third year, at about 10 years and again at the age of 16 or 17.

We have recently had the opportunity of observing what normal growth and development accomplished in a small group of children with thickened labial frenum. These children were part of a group reported on in an earlier study,[2] published in the AMERICAN JOURNAL OF DISEASES OF CHILDREN in 1936. In that report, we showed that a thickened labial frenum and its associated separation of the upper central incisors was more frequent in younger than in older children. It was suggested that the diminished incidence of the abnormality in

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1. Holt, L. E.: Growth as a Factor in Prognosis, J. A. M. A. **82**:1333 (April 26) 1924.

2. Schwartz, A. B., and Abbott, R. R.: The Rational Treatment of Abnormal Labial Frenum, Am. J. Dis. Child. **52**:1061 (Nov.) 1936.

older children was due to its natural obliteration, which followed the eruption of the full complement of permanent teeth.

In the previous study, comparative photographs of several instances of thickened labial frenum taken two and one-half years apart showed great improvement in the later photographs, even though the permanent teeth had not yet appeared at the time of the later pictures. Recent photographs, taken nine years after the last report, present the same children with a full complement of permanent teeth. In these photographs there is no sign of any abnormality, and a recession of the

Fig. 1.—*A*, K. B., aged 1 year, showing an abnormal thickening of the frenum with separation of the incisors; *B*, same child, aged 3½ years showing less thickening and a higher attachment of the frenum but the incisors still separated; *C*, same child, aged 12½ years, showing a normal frenum and normal alinement of teeth.

frenum attachment and an approximation of the central incisors have taken place without any intervening remedial measures, surgical or orthodontic.

Judging from a review of the dental literature of the last few years,[3] it appears that while the majority of oral surgeons do advise postponing

3. Kelsey, H. E.: When Is the Frenum Labium a Problem in Orthodontics? Am. J. Orthodontics **25**:124, 1939. Taylor, J. E.: Clinical Observations Relating to the Normal and Abnormal Frenum Labii Superioris, ibid. **25**:646, 1939.

Fig. 2.—*A*, C. M., aged 4 years, showing an exaggerated thickening and an abnormal attachment of the frenum, with separation of the deciduous incisors; *B*, same child, aged 6½ years, showing some improvement after the eruption of permanent incisors. *C*, same child, aged 15½ years, with a normal frenum and normal alinement of teeth.

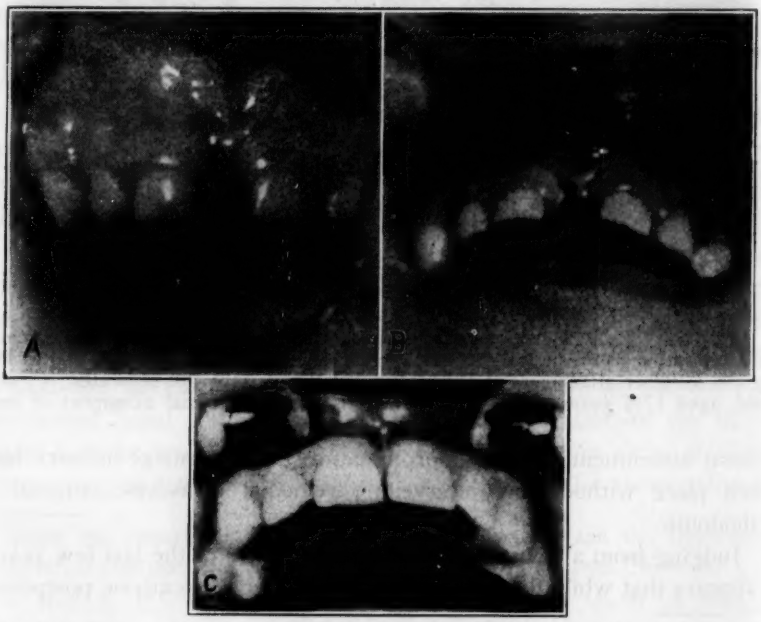

Fig. 3.—*A*, C. W., on whom surgical excision of the frenum had been done at the age of 2—photograph made at the age of 3 years; *B*, same child, aged 6, four years after the excision, still showing a wide separation of the incisors and considerable scar tissue resulting from the excision; *C*, same child, aged 15, showing a normal frenum and alinement, following growth and development.

operative intervention until after the appearance of the permanent teeth, some still regard surgical excision as indicated "when the frenum is abnormal." The reservation returns one to the original dilemma—when is the frenum abnormal?

Individual variations in structure and function are now generally recognized in all studies having to do with the appraisal of the child. Many of these variations ultimately disappear owing to the environmental or constitutional factors or that aggregate of factors included in the process of maturation.

It follows that a variation which at one age may be regarded as abnormal will prove to be, in the course of development and entirely without interference, normal.

During the intervening years since the first publication, we have seen no example of thickened labial frenum which the natural process of growth and development did not remedy.

Case Reports

PERNICIOUS ANEMIA IN CHILDHOOD

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PERNICIOUS anemia is essentially a disease of adults,[1] rarely seen under the age of 30 and beginning more commonly during the fifth decade. It is characterized by a macrocytic anemia, a related degeneration of the mucosa of parts of the gastrointestinal tract with a resultant complete achlorhydria and frequently a related degeneration of the central nervous system. It is primarily a deficiency disease, the gastrointestinal tract failing to yield the intrinsic factor, which unites with the extrinsic factor, from food, to form the erythrocyte maturation factor. This lack results in a maturation defect, an arrest of erythropoiesis at the megaloblastic level. There may be spontaneous remissions and relapses in the disease. Continuous treatment with preformed maturation factor results in reticulosis and in correction of the anemia but does not abolish the achlorhydria or bring about a regeneration of the gastric mucosa.

Closely related disorders exist which result from other deficiencies. In chronic digestive failures, such as celiac disease, an inadequate amount of the maturation factor may be absorbed, resulting in a macrocytic anemia. Other chronic intestinal disturbances may likewise result in failure of absorption. The achlorhydria seen sometimes with infections may result in absorption deficiencies. Hepatic disease may result in ineffective storage of the maturation factors and therefore may produce a picture similar to pernicious anemia. These are the common internal disorders, aside from the failure to secrete the intrinsic factor, which result in the development of a hematologic reaction similar to pernicious anemia.

In certain circumstances the diet may fail to yield enough extrinsic factor to maintain normal erythropoiesis. This is probably the commonest cause of macrocytic anemia in childhood. Often the effects of this deficiency are accentuated by concomitant infection. In this dis-

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1. Castle, W. B., and Minot, G. R.: Pathology: Physiology and Clinical Description of the Anemias, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 2, pt. 3, p. 631.

order, simple correction of the diet, temporary therapy with liver or even transfusions of blood may bring about a permanent remission.

In pernicious anemia, continuous remissions must be maintained by continuous treatment with the preformed erythrocyte maturation factor.

The purpose of this paper is to report a four year study of a child with pernicious anemia and to compare this study with the extant reports of pernicious anemia in childhood.

The occurrence of classic addisonian anemia in childhood must be rare. It is, in fact, so rare that such a standard reference text as "Holt's Diseases of Infancy and Childhood"[2] says, "It is doubtful, however, if pernicious anemia in a strict sense ever occurs in childhood. . . . The criteria of a specific response to liver extract and an achylia resistant to histamine have not been satisfied in a few reported cases." The "Atlas of the Blood in Children"[3] contains a foreword, which says, "There is essentially no blood disorder in adults that is not seen in children except addisonian pernicious anemia" and "Diseases of Blood"[4] says, "It is rare under 30 years of age and is said not to occur in children." Others comment in a similar vein.

Along with these views has arisen a concept that "pernicious-like anemia in childhood" is a disorder in which achlorhydria is only relative or impermanent and in which a short course of treatment with liver extract or even blood transfusions result in a permanent remission.[3]

The use of the term "pernicious anemia in childhood" should, however, be restricted to those cases which fulfil the criteria for the diagnosis of pernicious anemia already established for adults. These criteria are as follows:

1. Macrocytic anemia
2. Gastric achlorhydria resistant to histamine stimulation
3. Arrest of maturation in the bone marrow at the megaloblastic level
4. Specific response, i. e. reticulosis, following liver therapy
5. Necessity of continuous therapy to maintain a continuous remission.

Cases of anemia occurring during childhood in which liver extract has been effective have been reported by a number of investigators. Some of these investigators have presented their cases as instances of pernicious anemia in children, but many have been presented simply as cases in which there is a deficiency of the maturation factor.

2. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, ed. 11, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1939.

3. Blackfan, K. D., and Diamond, L. K.: Atlas of the Blood in Children, New York, The Commonwealth Fund, 1944.

4. Kracke, R. R.: Diseases of the Blood, ed. 2, Philadelphia, J. B. Lippincott Company, 1941.

Faber,[5] in 1928, reported on 3 unusual cases of macrocytic anemia. In 2 of these cases there was good response to liver extract. In another, while no improvement following liver therapy was shown, there was response to treatment with transfusions of whole blood. Two of the patients showed the presence of free hydrochloric acid through the period of observation, and the other, while achlorhydria did develop, had at the beginning of the study a low gastric acidity. The anemia in this case did not recur after the cessation of therapy. Similar cases were reported by Gerbasi,[6] Ducas and Jacquet,[7] Cooley and Lee,[8] Paez de la Torre,[9] Bachman,[10] Langmead and Doniach,[11] Adams and McQuarrie,[12] Debré Marie and associates,[13] Cole,[14] Fouts and Garber,[15] Calamari,[16] and Svastits.[17] Bachman's report reviewed all the cases of anemia occurring in infants under 1 year from 1906 to 1936.

In all these cases the patients were treated with and responded to liver extracts except in Faber's third case and in cases of Cooley and Lee, whose patients were treated by repeated transfusions of whole blood. In general, these patients showed hematologic pictures similar to pernicious anemia, and they showed a reticulosis with an increase in erythrocytes and hemoglobin following treatment with liver extract. They also, when studied, frequently showed an increase in gastric acidity

5. Faber, H. K.: Value of Liver Extract in Identifying and in Treating Certain Anemias of Infancy and of Childhood, Am. J. Dis. Child. **36**:1121 (Dec.) 1928.

6. Gerbasi, M.: Anemia perniciosa rigenerativa tipo Biermer in un lattante, Pediatria **37**:1343 (Dec. 15) 1929.

7. Ducas, P., and Jacquet, J. M.: Deux cas d'anémies graves précoces chez le nourrison, Arch. de méd. d. enf. **34**:420 (July) 1931.

8. Cooley, T. B., and Lee, P.: "Pernicious" Blood Pictures in Infancy, J. Pediat. **1**:184 (Aug.) 1932.

9. Paez de la Torre, J. M.: Anemia de Biermer observada en tres niños en el curso del año 1932, Semana méd. **2**:1822 (Dec. 15) 1932.

10. Bachman, A. L.: Macrocytic Hyperchromic Anemia in Early Infancy, Am. J. Dis. Child. **52**:633 (Sept.) 1936.

11. Langmead, F. S., and Doniach, I.: Pernicious Anemia in an Infant, Lancet **1**:1048 (May 1) 1937.

12. Adams, J. M., and McQuarrie, I.: Severe Functional Anemia in a Child, Resembling Pernicious Anemia of Adults, J. Pediat. **12**:176, 1938.

13. Debré Marie, J.; Lamy, M., and Ledoux-Lebard, G.: Un cas d'anémie pernicieuse observé chez un enfant de six ans, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:1286 (Dec.) 1939.

14. Cole, L.: Hyperchromic Anaemia in an Infant, Lancet **2**:759 (Dec. 20) 1941.

15. Fouts, P. J., and Garber, E.: Nutritional Anemia in an Infant Responding to Purified Liver Extract, Am. J. Dis. Child. **64**:270 (Aug.) 1942.

16. Calamari, A.: Anemia perniciosiforme in un lattante nato da donna affetta da anemia di biermer recidivante: Considerazioni etiopatogenetiche, Riv. di clin. pediat. **39**:38 (Jan.) 1941.

17. Svastits, P.: Anemia of the Pernicious Type in a Child, Orvosi hetil. **84**:179, 1940.

following treatment. There was no recurrence of the anemia in these cases, so far as could be determined, when the liver therapy was discontinued. Some of them, however, did not have sufficient follow-up studies for one to be certain of the point. The case of Svastits may, in fact, be one of pernicious anemia. He presented the case of a 16 month old infant, study of whom demonstrated a macrocytic anemia, megaloblastic arrest in the bone marrow, achlorhydria and a specific response to parenteral administration of liver, but the relapses, which also responded to liver therapy, he attributed to the mother's failure to maintain the child's diet, and he said that the child was well when last seen, apparently not requiring continual liver therapy.

Macrocytic anemia secondary to inadequate nutrition, such as occurred in the cases mentioned, are not rare, several instances having been encountered recently in children studied at Vanderbilt University Hospital, and Blackfan and Diamond[8] reported 15 such cases at the Children's Hospital, Boston. All the patients except 1 responded to a single course of liver extract.

Other cases reported as instances of pernicious anemia can be excluded as in them the condition accompanied specific infectious processes which were probably the cause of the anemia or it was due to diseases for which another causative mechanism is probable. Included in this group are the cases of Podwissotsky,[18] in which infection with Bothriocephalus latus was the probable cause; of Escherich,[19] in which the anemia was due to congenital syphilis; of Fiedeldij,[20] in which there was Taenia saginata infection; of Koch,[21] in which there was staphylococcic sepsis and of Christiansen,[22] which was probably a case of congenital hemolytic icterus.

Another group of cases reported as instances of pernicious anemia can probably be excluded by the fact that the anemia was inadequately studied in life and/or that the diagnosis is based on postmortem observation. The cases of Monti and Berggrün,[23] Theodor,[24] von

18. Podwissotsky, H.: Zur Casuistik der mit Bothriocephalus latus in Verbindung stehenden Form der progressiven perniciösen Anämie, Jahrb. f. Kinderh. **29**:223, 1889.

19. Escherich: Ueber perniziöse Anämie im Kindesalter, Wien. klin. Wchnschr. **5**:193, 1892.

20. Fiedeldij, C. E.: Anæmia perniciosa bij een Kind, Jahrb. f. Kinderh. **43**:288, 1896.

21. Koch, G.: Ueber perniziöse Anämie und extramedulläre Blutbildung im Säuglingsalter, Jahrb. f. Kinderh. **71**:140, 1910.

22. Christiansen, T.: A Case of Pernicious Anemia in a Child with a Peculiar Course, Hospitalstid. **70**:875 (Sept. 15) 1927.

23. Monti, A., and Berggrün, E.: Die chronische Anämie in Kindesalter, Leipzig, F. C. W. Vogel, 1892.

24. Theodor, F.: Ein Fall von progressiver perniciöser Anämie im Kindesalter, Arch. f. Kinderh. **28**:321, 1900.

Starck,[25] von Seht[26] and of Templeton[27] were inadequately studied to establish a diagnosis of pernicious anemia. The case of Kusunoki,[28] and the second case of Brückner[29] were labeled pernicious anemia primarily on the basis of postmortem changes and on criteria which would not now serve as adequately establishing the diagnosis.

There are, finally, a group of cases in which the diagnosis of pernicious anemia cannot be excluded with certainty though the evidence is not adequate to accept them as proved cases. Included in this group is the case of Hotz,[30] who described an 11 year old girl with macrocytic anemia, relative leukopenia and thrombopenia; she had one spontaneous remission followed by a fatal relapse. There was no gastric analysis, and the case was observed prior to the era of liver therapy. The first case in Brückner's study[29] was that of a 10 year old girl who had a macrocytic anemia with achlorhydria and on whom the postmortem observations were compatible with pernicious anemia, but this case was also in the "pre-liver" era.

It is fair to state that in general little can be expected of the literature in the years before the introduction of liver therapy, when many diseases were called pernicious anemia simply because they were severe or refractory.

We were able to find in the literature only 2 cases which satisfactorily fulfil criteria establishing them as indubitable cases of pernicious anemia in childhood and a third case which might be of pernicious anemia. These cases warrant a brief review.

Pohl,[31] in 1940, reported the study of a 13 year old girl who had a macrocytic anemia of six months' duration. She was pale, with a yellow tint to the skin, and had a somewhat smooth tongue and a slightly enlarged heart with a hemic murmur. The blood picture revealed, in addition to a macrocytic anemia, normoblasts and a moderate leukopenia. She had a histamine-resistant achlorhydria, and a single trial failed to show any intrinsic factor in the gastric juice. There was no demonstrable abnormality of the gastrointestinal tract on

25. von Starck, W.: Die basophile Granulation (Punktierung) der roten Blutkörperchen im embryonalen Blut und die anämischen Zustanden im Kindesalter, Jahrb. f. Kinderh. **69**:254 1909.

26. von Seht, L.: Ueber kryptogenetische Biermerche Anämie im Kindesalter, Ztschr. f. Kinderh. **18**:15, 1918.

27. Templeton, W. L.: Pernicious Anæmia in a Child, Lancet **2**:1221 1939.

28. Kusunoki, M.: Die perniziöse Anämie im früheren Kindesalter, Cor.-Bl. f. schweiz. Aérzte **44**:833, 1914.

29. Brückner, M.: Zur Kasuistik der Biermerschen Anämie im Kindesalter, Jahrb. f. Kinderh. **114**:370 (Dec.) 1926.

30. Holtz, A.: Ueber Anaemia perniciosa und perniciösa-ähnliche Anämien im Kindesalter, Jahrb. f. Kinderh. **105**:161, 1924.

31. Pohl, C.: Ueber perniziöse Anämie im Kindesalter, Monatschr. f. Kinderh. **84**:192, 1940.

roentgenographic examination, and there was no apparent hepatic disease.

Treatment with liver brought about a characteristic response with a shift of the color index from 1.18 through 1.54, then to 0.96 and ending at 1.01. The achlorhydria persisted.

Her course was followed through one severe relapse, which occurred when parenteral liver therapy was refused. With this relapse she again had smoothness of her tongue. She also had numbness and tingling of her fingers. To parenteral liver therapy she again responded in characteristic fashion. With continuous therapy, she was well at the end of a four year study period.

It is of interest to note that there was in this patient a shift from a macrocytic anemia to a relative state of hypochromia following the maturation of large numbers of new red blood cells.

Andreasen, in 1941, reported a case of macrocytic anemia in a 14 year old girl. She had achlorhydria and responded to liver extract. The report appeared in a journal not now available in this country, and the abstract of the article by Wallgren [32] is inadequate to evaluate the case critically.

Dedichen,[33] in 1942, reported a case of macrocytic anemia in a child of 13 months. Examination of the child's bone marrow showed an arrest of erythopoiesis at the megaloblastic level. She had achlorhydria following an Ewald test meal.[34] A specific response to liver therapy was obtained. Repeated relapses occurred over a period of three years whenever liver therapy was withheld. The child's normal growth and development when on liver therapy and the absence of observations suggestive of celiac disease or other forms of chronic indigestion ruled out the possibility of other intrinsic disease of the gastrointestinal tract. The hepatic function was normal, as far as could be judged by clinical observation and hepatic function tests.

The cases of Pohl and Dedichen seem to us to satisfy adequately the criteria for the diagnosis of pernicious anemia.

To these cases we wish to add our own case of pernicious anemia, that of a child followed from the age of 13 months to her present age (5½ years), whose anemia, historically, dated back to the age of 8 months.

REPORT OF A CASE

A. A. was admitted to the pediatric service of Vanderbilt University Hospital on Nov. 25, 1940, at the age of 13 months, because of diarrhea and pallor.

32. Andreasen, J. P.: Pernicious Anemia, Ugesk. f. læger **103**:783 (June 12) 1941; abstracted, Am. J. Dis. Child. **66**:321 (Sept.) 1943.

33. Dedichen, J.: Anémie à type pernicieux chez un enfant de 9 mois, Acta med. Scandinav. **111**:90, 1942.

34. Histamine stimulation was not used.

At the age of 7 months she became ill with pneumonia. Spontaneous recovery occurred within a week. Shortly after this episode it was observed that she had a noticeable pallor. From 10 months on she lost weight and her pallor seemed to increase.

At 11 months she began to have diarrhea, fifteen to twenty yellow-green stools daily. The stools contained mucus, pus and occasional flecks of blood. The diarrhea subsided after a week, and the stools gradually became normal. Her pallor, however, again seemed to increase. She was weaned from the breast because of failure to nurse well and put on a buttermilk formula, without significant improvement, and soon the breast feedings were resumed. She lost more weight, and the diarrhea recurred and persisted until admission, with an average of ten to fifteen stools daily. Three weeks before admission she became "swollen." Puffiness of the hands, feet and eyelids was noted. The puffiness disappeared and she became "dry" just before admission.

The family history revealed the following significant facts: 1. The father had asthma. 2. There had been four pregnancies, with 2 living siblings. 3. One child died at the age of 3 years from diarrhea and anemia.

The past history, aside from the chronicled events, was not remarkable. She had been principally breast fed and had received no supplements of vitamins.

Physical Examination.—The patient was an extremely emaciated, waxy pale, chronically ill infant who was irritable. Her temperature was 101.6 F., respiration rate 48 and pulse rate 130 and she weighed 12 pounds 10 ounces (5,725 Gm.). There was deficient tissue turgor, with a loose inelastic skin. The skin showed two types of lesions, an excoriated papular dermatitis characteristic of scabies and generalized petechiae with a few small ecchymotic areas.

The mucous membranes were extremely pale. A generalized shotty lymphadenopathy was present. The eyes, ears, mouth and nose were normal. The respiratory system was clear. The heart was enlarged to the left, and a loud systolic murmur was heard over the precordium. The liver and spleen were slightly enlarged.

Following are the results of laboratory studies made on the day of admission. Urinalysis revealed no albumin, no sugar, and the sediment of occasional granular casts. Examination of the blood showed: 2 Gm. of hemoglobin per hundred cubic centimeters, 810,000 red cells per cubic millimeter,[35] a color index of 0.82 and 56,700 reticulocytes per cubic millimeter, with the presence of a few nucleated red cells. There were 62,000 white blood cells with 90 per cent lymphocytes and 8 per cent smudges. The stained films also showed pronounced anisocytosis and poikilocytosis and an almost total absence of platelets. The total serum proteins were 6.6 Gm., with albumin 4.4 and globulin 2.2 Gm. The p_H of the blood was 7.41, the carbon dioxide combining power 42.8 volumes per cent and the nonprotein nitrogen 75 mg. per hundred cubic centimeters. Cultures of stool yielded Shigella paradysenteriae, Flexner group. A culture of the blood, not confirmed by later cultures, yielded a scanty growth of Streptococcus viridans.

This picture was thought to represent: (1) acute bacillary dysentery, (2) anemia, secondary to iron starvation and repeated infections, (3) rickets, with other vitamin deficiencies and (4) thrombopenic purpura, secondary or associated with leukemia or another primary blood dyscrasia—the leukemia appearing to be most probable.

Course in Hospital, First Admission.—A vigorous treatment regimen was started immediately. The patient was given blood transfusions and supplements of vitamin A, thiamine hydrochloride, nicotinic acid, riboflavin, ascorbic acid and

35. A check of the red blood cell count showed 910,000 cells.

vitamin D. After a preliminary starvation of twelve hours, the feeding of buttermilk with 10 per cent added sugar was begun, and she was given sulfathiazole for the enteritis. There was a gradual improvement in her general condition, though she continued to have two or three loose stools daily for six weeks. The feedings were liberalized after the first ten days. During the first eleven weeks in the hospital there was a net gain of 3 pounds (1,360 Gm.), and during a second period, four weeks before discharge, there was a gain of 5 pounds (2,265 Gm.).

During the first period of her stay she was irritable and at times had to be fed by gavage and, though her hemoglobin content and red blood cell count were maintained by blood transfusions at levels of 9 to 16 Gm. per hundred cubic centimeters and 3,000,000 to 6,000,000 cells per cubic millimeter, respectively, she continued to have lymphocytosis and thrombopenia. A gastric analysis performed at the end of the ninth week showed achlorhydria. This was confirmed after histamine stimulation two weeks later. With this combination of conditions, continued malnutrition—her skin hung in folds—a tendency for the anemia to recur when transfusions were not repeated, an abnormal lymphocytosis and a constant thrombopenia, we were of the opinion that she might respond to liver extract. On Feb. 12, 1941, she was started on liver extract, 0.5 cc. of concentrated extract, equivalent to 7.5 units, every four days, a total of 3 cc. (45 units) being given over a period of twenty-one days. The institution of this therapy resulted in an immediate improvement; she ate better, she changed from a picture of abject misery to a playful happy child, and the tendency for anemia to develop disappeared. A peak of 574,000 reticulocytes per cubic millimeter (14 per cent of 4,100,000 red blood cells) was obtained in eight days.

It is of interest that she had definite lymphocytosis throughout the period except after the institution of liver therapy and immediately after some of the transfusions. The leukocytosis which was present throughout was not always explainable.

Chart 1 summarizes her course in the hospital as related to the anemia and its response to treatment. In chart 1 and in subsequent charts, the ratio between the hemoglobin level and the red blood cell level is such that the values coincide when the cells are isochromic, the hemoglobin tracing being highest when there is macrocytosis while the red cell tracing ascends when there is hypochromia.

In chart 1 it is of interest to note that there was never during this period a really significant macrocytosis.

Other laboratory studies during her admission showed: (1) low serum protein levels; (2) urine normal throughout; (3) a nonprotein nitrogen of 75 mg. per hundred cubic centimeters at the time of admission, falling gradually to normal after adequate hydration; (4) reaction to Kahn test negative; (5) reaction to old tuberculin (0.1 mg.), negative; (6) roentgenograms of the long bones showing atrophic changes, but no changes specific for deficiency disturbances.

She was discharged on March 15, at the end of fifteen weeks' hospitalization, apparently well.

The discharge diagnoses were: (1) acute bacillary dysentery with severe malnutrition; (2) anemia secondary to infection and malnutrition; (3) thrombopenic purpura, infectional, and (4) scabies.

Following discharge, she was seen at the end of a month, still apparently well. On June 10, 1942, fourteen months later, at the age of 31 months, she was readmitted.

During the interval she had remained well, had taken a varied, fairly adequate diet and had gained in weight, a net amount of 2 pounds (960 Gm.). Suddenly

three weeks before admission, about May 20, she became ill. She became pale but did not have any definite symptoms except those related to purging associated with treatment for supposed worms. Three days before admission she had a fever and abdominal pain and seemed much sicker. The day before admission she had a few loose watery stools. The family had not noted any changes in her skin.

Examination at the time of admission revealed a pale, poorly nourished girl who appeared to be chronically ill. The skin showed a moderate number of petechiae generally distributed and a few small ecchymotic areas. There was no significant enlargement of lymph nodes, and the spleen was not large. The heart, as at the previous admission, was enlarged and overactive. A loud blowing systolic murmur was heard over the entire precordium.

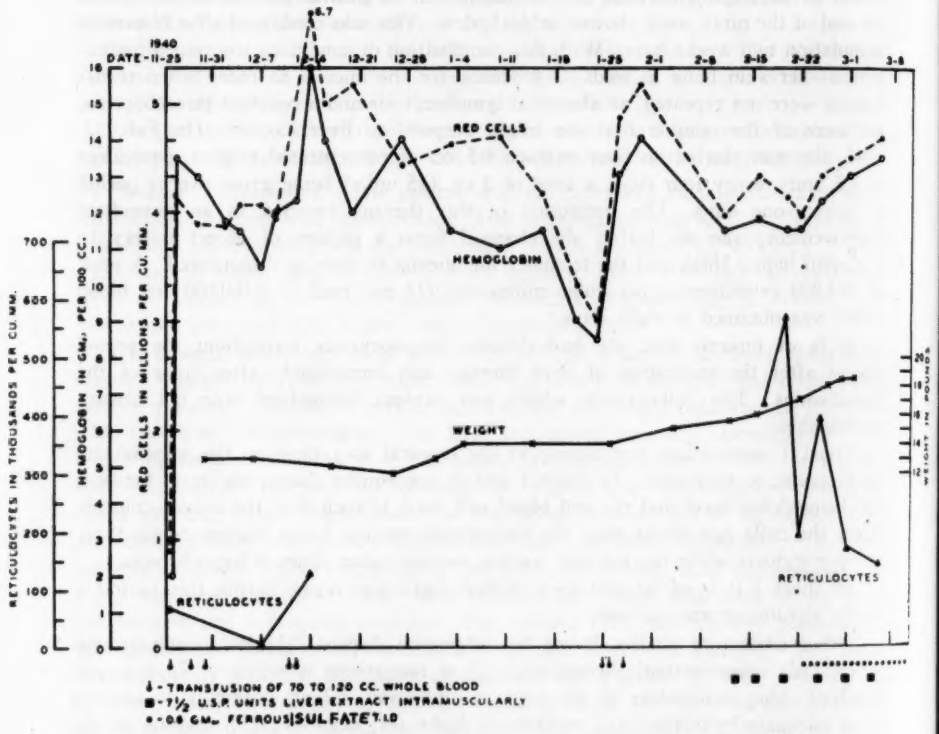

Chart 1.—Studies showing changes in the blood and in the body weight of the patient before and after liver therapy during the first admission.

Following are the results of laboratory studies at admission: The urine was normal. An examination of the blood revealed 6.8 Gm. of hemoglobin per hundred cubic centimeters, 1,470,000 red cells per cubic millimeter, a color index of 1.5, and 7,350 reticulocytes per cubic millimeter (0.5 per cent). There were 7,800 white cells, with 86 per cent lymphocytes, 10 per cent segmented polymorphonuclear leukocytes, 2 per cent blast cells, 1 per cent monocytes and 1 per cent basophils. The smears also showed noticeable variation in the size and shape of the red cells and 2 to 3 nucleated red cells per hundred white cells; results of a fragility test were normal, and the icteric index was 10 (van den Bergh indirect test).

Diagnoses entertained at the time of admission were (1) that she had leukemia and that her course had represented merely an extraordinary remission after transfusions (this seemed unlikely) and (2) that she had a primary anemia due to a deficiency of maturation factors, possibly only precipitated by infection (this seemed most likely).

Course During the Second Admission.—After preliminary studies had been completed and after the patient had received enough blood to stop the purpuric manifestations, iron therapy was begun. She had a low grade fever, with temperatures of 100 to 101 F. for three days, and continued to have a few loose stools for sixteen days. The administration of iron preparations over a period of eleven

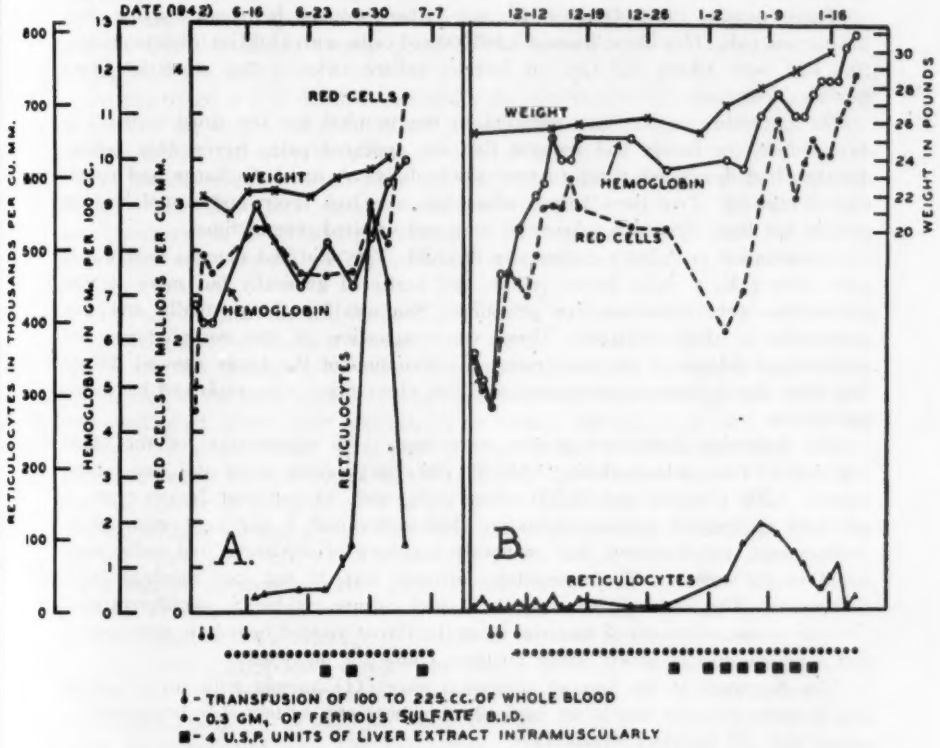

Chart 2.—*A* (second admission) and *B* (third admission), further studies showing later changes in the blood and body weight of the patient after liver therapy.

days failed to bring about reticulosis or an increase in red blood cells or hemoglobin. On June 25, she was given additional therapy in the form of injections of liver extract. On June 30, reticulosis, with a count of 552,000 reticulocytes per cubic millimeter (19 per cent) was observed.

Again it should be noted that during this admission there was no significant macrocytosis except on the first observation, and this observation cannot be accepted without reservation.

Chart 2A is a graphic representation of the hematologic studies and antianemic therapy during the second admission.

Though there were a few reticulocytes during the first two weeks after this admission, their presence was not accompanied with a change in the blood picture, and no real improvement occurred until liver therapy was instituted. The diarrhea stopped the day of the first injection of liver.

She was discharged greatly improved at the end of four weeks. The diagnosis still seemed uncertain, but it appeared most likely that an infection was responsible for precipitating a failure of cell maturation.

When seen two weeks after discharge, July 22, she was well. Her weight had increased to 29 pounds (13,154 Gm.), a gain of 6 pounds (2,722 Gm.) in six weeks. Studies of the blood showed 4,100,000 red cells, 14.5 Gm. of hemoglobin and 27,000 white cells, with 62 per cent lymphocytes. She was instructed to return if she did not remain well.

Three months later, October 15, her father brought her back, saying that she seemed pale. Her blood showed 3,040,000 red cells, with 11.0 Gm. of hemoglobin. She had been taking 0.3 Gm. of ferrous sulfate twice a day since in June; this was continued.

On December 6, she was admitted to the hospital for the third time. Ten days before, the family had thought that she appeared pale. Seven days before, diarrhea had developed, three to four stools daily. A nasal discharge and cough also developed. Two days before admission, she had fever and complained of pain in her legs. She also refused all food and vomited several times.

Examination revealed a chronically ill child. The skin and mucous membranes were very pale, a waxy lemon yellow, and scattered generally but more on the extremities were numerous fine petechiae. She was breathing rapidly and was apparently in slight distress. There was congestion of the nasopharynx and redness and fulness of the ear drums. Examination of the lungs showed diffuse fine rales due to bronchopneumonia, and this observation was confirmed by roentgenograms.

The following laboratory studies were made. An examination of the blood revealed 5.7 Gm. of hemoglobin; 1,850,000 red cells; a color index of 1.2 no reticulocytes, 8,200 platelets and 16,800 white cells, with 94 per cent lymphocytes, 5 per cent segmented polymorphonuclear leukocytes and 1 per cent eosinophils. Anisocytosis, poikilocytosis and moderate numbers of nucleated red cells were noted in the smears. The nonprotein nitrogen was 32 mg. per hundred cubic centimeters. The icteric index was 6. A stool culture yielded S. paradysenteriae, Flexner group. Cultures of material from the throat yielded hemolytic streptococci and a pneumococcus which, while virulent, could not be typed.

The diagnoses at the time of admission were: (1) anemia with thrombopenia and granulocytopenia due to an inadequate hemopoietic system, (2) bronchopneumonia and (3) bacillary dysentery.

Course During the Third Admission.—She was given small amounts of liquids, fruit juices and milk at intervals of two hours. Sulfathiazole was given by mouth, and bilateral myringotomy was performed. Her temperature rose to 104 F. shortly after admission and then fell by rapid lysis to normal twenty-four hours later. The continuous administration of iron preparations, which she had received prior to this admission, was reinstituted after a lapse during the first four hospital days and was continued throughout the admission. There was no resultant change in the blood picture. After eighteen days on iron therapy she was given crude liver extract by intramuscular injection.

Nine days after liver therapy was instituted there was a reticulosis with 186,000 cells per cubic millimeter (6 per cent of 3,100,000 red cells), followed by a rapid rise in the hemoglobin level and the red cell count. The platelets, which had not been

higher than 70,000 per cubic millimeter, rose to 500,000, and the polymorphonuclear leukocytes in the circulating blood increased. It is of interest to note that the macrocytosis and high color index persisted throughout. A gastric analysis after improvement had occurred showed the persistence of achlorhydria.

The hematologic changes before and after therapy are shown in chart *2B*.

She was discharged on Jan. 19, 1943, much improved.

The discharge diagnoses were: (1) pernicious anemia, (2) bronchopenumonia, and (3) bacillary dysentery.

We were at this time certain that our patient satisfied the requirements for a diagnosis of pernicious anemia, but we knew of no instance of pernicious anemia occurring in a child and thought that we might still be dealing with a process precipitated only by infection. Against this view were the degree of anemia without evident hemolysis which was present so soon after the onset of infection and the fact that pallor usually preceded the acute infection which precipitated hospitalization.

At discharge it was decided that while she would probably need liver therapy continually we would withhold it and readmit her for a better controlled study as soon as she had another relapse.

On March 10, seven weeks after discharge, she was well and her blood showed 5,210,000 red cells, 13.8 Gm. of hemoglobin and 21,000 white cells, with 68 per cent lymphocytes, 30 per cent polymorphonuclear leukocytes, 1 per cent eosinophils and 1 per cent basophils. The platelets appeared normal, and there were no nucleated red cells.

On June 24, she was still in good health. No studies of the blood were made.

On June 6, 1944, she was brought back for the fourth admission. Two months before, she had become pale. After a month of gradually increasing pallor, she was carried to the local physician, who gave the patient an oral antianemic preparation containing some liver extract. The family thought that she started to improve, but a sore throat developed, she rapidly lost ground and a week before admission began to have diarrhea, although this ceased after a day or two. She was not acutely ill with infection at the time of admission.

Examination showed a well nourished and well developed child, not ill. She was very pale, and there was a yellow tint to her skin. No purpura was present. There was no adenopathy. Her teeth were extremely carious. The heart, as on previous admissions, was overactive, and a loud blowing systolic murmur was audible. There was no evidence of disease of the central nervous system.

Laboratory studies were carried out over a period of two weeks. The urine was normal. The blood contained 4.5 Gm. of hemoglobin per hundred cubic centimeters and 1,620,000 red cells per cubic millimeter (color index 0.93), of which 32,400 were reticulocytes. The percentage of packed cells was 17; the mean corpuscular volume, 104 cubic microns; the mean corpuscular hemoglobin, 27.7 micromicrograms, and the mean corpuscular hemoglobin concentration, 26.5 per cent. The white cell count was 11,500, with 53.5 per cent lymphocytes, 24.5 per cent polymorphonuclear leukocytes, 3 per cent stab forms and 1 per cent eosinophils. There were poikilocytosis and anisocytosis with many macrocytes. The polymorphonuclear leukocytes were hypersegmented. There were 2 erythroblasts and 1 normoblast per hundred leukocytes, 230 and 115 per cubic millimeter, respectively and 176,000 platelets. The icteric index was 12 (van den Bergh indirect test). Sternal marrow obtained by aspiration yielded: 21 per cent megaloblasts, 5 per cent normoblasts, 5 per cent myeloblasts, 3 per cent premyelocytes, 11 per cent myelocytes, 2.5 per cent juvenile polymorphonuclear leukocytes, 3.5 per cent stab forms, 14 per cent segmented forms, 2 per cent megakaryocytes and 20 per cent

lymphocytes, the remainder being unidentifiable; there was a marked arrest of erythropoiesis at the megaloblastic level. This bone marrow picture was indistinguishable from that of adults with pernicious anemia.

The results of an analysis of gastric contents were as follows:

	Free HCl, Degrees	Combined HCl, Degrees
Fasting	0	6
After alcohol	0	3.8
After histamine	0	6.2

An examination of the stool showed no pathogenic bacteria or parasites.

On culture of materials from the throat no pathogenic organisms were demonstrated.

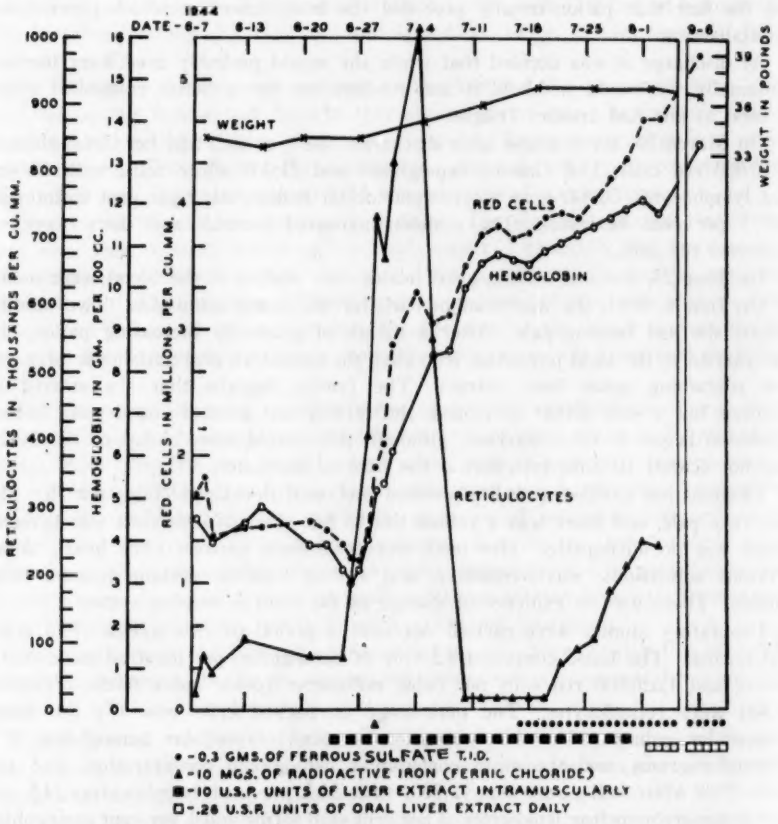
1944
DATE - 6-7 6-13 6-20 6-27 7-4 7-11 7-18 7-25 8-1 9-6
WEIGHT
RED CELLS
HEMOGLOBIN
RETICULOCYTES
RETICULOCYTES IN THOUSANDS PER CU. MM.
HEMOGLOBIN IN GM. PER 100 CC.
RED CELLS IN MILLIONS PER CU. MM.
WEIGHT IN POUNDS
• - 0.3 GMS. OF FERROUS SULFATE T.I.D.
▲ - 10 MGS. OF RADIOACTIVE IRON (FERRIC CHLORIDE)
■ - 10 U.S.P. UNITS OF LIVER EXTRACT INTRAMUSCULARLY
□ - .26 U.S.P. UNITS OF ORAL LIVER EXTRACT DAILY

Chart 3.—Changes in the blood and body weight of the patient before and after liver therapy during the fourth admission.

This picture seemed to fit well with the concept of the patient's having pernicious anemia in relapse except that the color index of the red blood cells was low. This will be commented on later.

During the period of observation there was some fluctuation in her blood counts, but generally there was a steady degree to 1,470,000 red cells, and 3.9

Gm. of hemoglobin. Use of liver extract was then started, 10 units by intramuscular injection every forty-eight hours. The peak of her responses was reached in ten days, when she showed 987,000 reticulocytes per cubic millimeter (30.4 per cent of 3,280,000 cells). The changes in the blood picture during this admission are shown in chart 3.

It is of interest first to note that during this study there was never macrocytosis and that the color index was not, except on two of the earlier determinations, as high as 1.

The reason for this lack of macrocytosis in pernicious anemia in a profound relapse is demonstrated in a study of the absorption of iron carried out by Dr. P. F. Hahn. On the fifth day after therapy with liver extract was begun, she was given 10 mg. of radioactive ferric chloride. Subsequent studies on the amount of radioactive iron in the blood showed that approximately 25 per cent of the test dose had been absorbed and utilized. A patient with pernicious anemia having adequate iron stores would not have absorbed and utilized more than 2 per cent of the test dose of iron.[36] It is apparent from this study that she had a deficiency of iron in addition to an arrest of maturation.

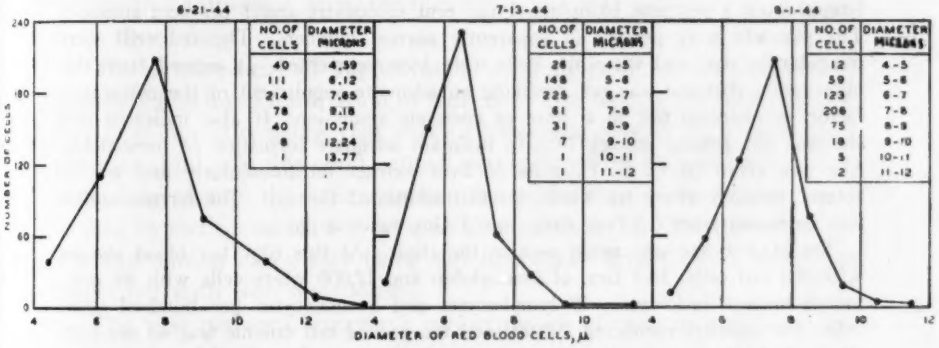

Chart 4.—Variations in the diameter of the patient's red cells during the course of therapy (Price-Jones curves) during the fourth admission.

The Price-Jones cell diameter distribution curves made as the patient's treatment progressed are of interest. These curves made before therapy, after liver therapy with its maximum response and finally after the administration of iron preparations had been instituted are shown in chart 4.

It may be noted that before treatment the apex of the curve is at 7.7 microns, with a few cells scattered up in the range of 12 to 13 microns. After the peak of reticulosis and the elaboration of large numbers of new cells and after a relative increase in iron deficiency has occurred, the apex of the curve shifts to 6.5 microns, and only 1 cell was observed with a diameter greater than 11 microns. With the addition of iron therapy, the apex of the curve shifts back to 7.5 microns. There was also a secondary increase in reticulocytes.

By the fifty-eighth hospital day, the fortieth day after the initiation of liver extract, the red blood cell level had reached 4,700,000 per cubic millimeter and the hemoglobin level 11.8 Gm. No transfusions were used. Gastric analysis still

36. Balfour, W. M., and others: Radioactive Iron Absorption in Clinical Conditions, J. Exper. Med. **76**:15 (July) 1942. Hahn, P. F., Vanderbilt University, Nashville, Tenn.: Personal communication to the authors.

showed a complete absence of free hydrochloric acid after the administration of 0.01 mg. of histamine per kilogram of body weight. She left the hospital on August 5, the sixtieth day, in radiant health.

She was put on a regimen at discharge which would provide an adequate diet and a daily supplement of the maturation factor equivalent to 0.27 unit per day in the form of liver extract given by mouth.[37] She also received 0.3 Gm. of ferrous sulfate daily and 2 cc. of dilute hydrochloric acid with each meal. Oral therapy was instituted because she lives in a rural area where it is not easy to get intramuscular injections and returning to the clinic for the injections seemed impracticable.

After discharge from the hospital, she remained well. She was seen September 6, at which time her hemoglobin value was 13.5 Gm. per hundred cubic centimeters with 5,860,000 red blood cells per cubic millimeter.

On Jan. 5, 1945, she again reported. Her health had remained good. Her blood showed 13 Gm. of hemoglobin, 4,800,000 red cells, no reticulocytes and 18,000 white cells, with a normal differential count.

On March 4, her blood showed 9.2 Gm. of hemoglobin, 3,420,000 red cells and 10,650 white cells, with 67 per cent polymorphonuclear leukocytes, 29 per cent lymphocytes, 1 per cent basophils, 1 per cent monocytes and 1 per cent smudges. The platelets were present in apparently normal numbers. The red cells were irregular in size, and the white cells were hypersegmented. It seemed from this observation that she was not receiving an adequate supplement of the maturation factor to maintain her in a state of complete remission. It also indicated that she was not getting enough iron to maintain adequate formation of hemoglobin. She was given 10 U. S. P. units of liver extract intramuscularly and was to return regularly every six weeks for this additional therapy. The ferrous sulfate was increased from 0.3 Gm. daily to 0.3 Gm. twice a day.

On May 9, she was again seen in the clinic. At this time her blood showed 4,100,000 red cells, 13.3 Gm. of hemoglobin and 12,000 white cells with 44 polymorphonuclear leukocytes, 49 lymphocytes and 5 monocytes per hundred white cells; the platelets numbered 200,000 and the packed cell volume was 43 per cent.

A fluoroscopic examination of the upper gastrointestinal tract showed the stomach and small intestine to be anatomically normal. When last seen, on June 20, 1945, she had 5,200,000 red blood cells per cubic millimeter with 15 Gm. of hemoglobin per hundred cubic centimeters.

COMMENT

This patient presents a complex picture of an anemic state. The continued achlorhydria; the arrest of cell maturation at the megaloblastic level in the bone marrow; the associated granulocytopenia, thrombopenia, and, at times, a macrocytic character to the anemia; the specific response to the erythrocyte maturation factor in the form of liver extract; the absence of a significant gastrointestinal lesion or parasites and the apparent absence of hepatic disease, and, finally, the demonstration of repeated relapses and specifically induced remissions make it appear that she has addisonian pernicious anemia. At least she has an anemia which if demonstrated in a woman of 50 years would unquestionably be called pernicious anemia. If one wishes to call this anemia by some other name

37. Valentine's liver extract for oral administration, 1 U. S. P. unit per 45 cc.

because of the patient's age, a new disease entity will have to be accepted to take care of this case and the cases of Pohl and Dedichen. Such a step seems unwaranted, at least until more is known of the etiology of pernicious anemia.

There is, however, in this study a clearcut demonstration that this patient has a continuing iron deficiency. This deficiency was not corrected by continuous administration of iron preparations at the level of 0.3 Gm. of ferrous sulfate daily, as is evidenced by the developing hypochromic anemia revealed on March 4, 1945, after the patient had been receiving iron continuously for over seven months. This is also illustrated by a comparison of the blood pictures shown at the various admissions. Only at the time of the third admission, when her iron stores had been maintained by administration of ferrous sulfate at the level of 0.3 Gm. twice daily for more than five months, was there a real macrocytosis. This macrocytosis was increased during the period prior to liver therapy during this admission when the ferrous sulfate was increased to 0.3 Gm. three times daily.

The development of hypochromia in adult patients with pernicious anemia following the initiation of treatment is a recognized phenomenon, and it is not surprising that this development would be greater in a growing child. In this child, whose iron metabolism may be poorer than normal because of the defect causing the achlorhydria, one might expect to find hypochromia as well as a lack of maturation. Further study of this and similar cases may bring out important details of the problems associated with iron metabolism.

The past pediatric literature on pernicious anemia in childhood has been confused by the absence of adequate criteria for the establishment of the diagnosis and the subsequent inclusion of many conditions of diverse causation as pernicious anemia. These fallacious inclusions include cases of anemia secondary to infection, secondary to parasitism with helminths and secondary to celiac disease. This confusion has been less since the introduction of liver therapy, but it has continued to the present time. The criteria [38] mentioned by Parsons and Hawksley [39] for the diagnosis of pernicious anemia in childhood are inadequate and would permit the inclusion of the relatively common macrocytic anemias due to malnutrition, deficiency of the extrinsic factor and other causes.

The use of the term "pernicious anemia in childhood" should be restricted, as it is in general medicine, to those cases of macrocytic anemia in which there is a complete and continuous achlorhydria, in which

38. These criteria are: (1) a high indirect van den Bergh reaction; (2) pronounced poikilocytosis: (3) almost complete absence of free hydrochloric acid in the gastric juice, and (4) a reticulosis with liver extract.

39. Parsons, L. G., and Hawksley, J. C.: Studies of Anaemias in Infancy and Early Childhood, Arch. Dis. Childhood **8**:184, 1933.

the patient shows a specific response to liver therapy and in which continual therapy is required to maintain the patient in a state of remission. The tendency for the hematologic picture to be confused by a concomitant iron deficiency would seem to be more important in children than in adults, but this should present no serious diagnostic difficulty.

SUMMARY

The literature concerning anemia in childhood of a macrocytic nature in which there is a response to liver therapy has been reviewed. The review covers the foreign literature only until 1942.

The cases reported have been analyzed and have been separated into two groups, those having a complete picture of pernicious anemia and those having the hematologic picture of pernicious anemia but not requiring continual treatment to maintain a state of remission and presumably not due to a deficiency of the intrinsic factor.

A case study of a 5 year old child for whom the laboratory observations and the clinical course satisfy stringent criteria for the diagnosis of pernicious anemia is presented.

This makes the third case of pernicious anemia occurring in childhood and the second occurring in infancy.

ERYTHROPHAGOCYTOSIS IN ACUTE HEMOLYTIC ANEMIA OF THE NEWBORN

A Report of Three Cases

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ST. LOUIS

THE phagocytic activity of the leukocytes of the blood against erythrocytes has been observed and reported by a number of authors, the first being von Ehrlich,[1] in 1891, in a case of paroxysmal hemoglobinuria. He was followed by Connal,[2] in 1912, who was the first to describe it in infants and children. His report dealt with cases of malaria. Abt [3] was the first to describe the phenomenon in anemia of the newborn. Since Abt's case was published, 6 more cases of erythrophagocytosis in anemia of the newborn have appeared in the literature, the most recent being the 3 cases described by Wyatt, Cooper and Groat.[4] It is the purpose of this paper to add 3 more cases of erythrophagocytosis in anemia of the newborn to the 7 already described.

BLOOD DISEASES SHOWING ERYTHROPHAGOCYTOSIS

It is not the purpose of this paper to review the literature published about this phenomenon, but one should tabulate the conditions in which it has been found. These are: in paroxysmal hemoglobinuria,[1] malaria,[2] anemia of the newborn,[5] severe pernicious anemia [6] and severe secondary anemia,[7] following splenectomy,[8] in potassium chlorate poisoning,[9] myelo-

From the Department of Pediatrics of St. Louis University.

1. von Ehrlich, P.: Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes, Berlin, A. Hirschwald, 1891, p. 110.

2. Connal, A.: Auto-Erythrophagocytosis in Protozoal Diseases, J. Path. & Bact. **16**:502, 1911-1912.

3. Abt, A. F.: Mononuclear Erythrophagocytosis in the Blood of a New-Born Infant, Am. J. Dis. Child. **42**:1364 (Dec.) 1931.

4. Wyatt, T. C.; Cooper, M. B., and Groat, W. A.: Erythrophagocytosis in Anemia of the New Born: Report of Three Cases, Am. J. Dis. Child. **56**:1319 (Dec.) 1938.

5. Abt.[3] Wyatt, Cooper and Groat.[4]

6. Hoff, F.: Untersuchungen über das weisse Blutbild und seine biologischen Schwankungen, Krankheitsforschung **4**:89, 1927.

7. Rowley, M.: A Fatal Anemia with Enormous Numbers of Circulating Phagocytes, J. Exper. Med. **10**:78, 1907.

8. Domagk, G.: Ueber das Auftreten von Endothelien im Blute nach Splenektomie, Virchows Arch. f. path. Anat. **249**:83, 1924.

9. Lange, F.: Ueber einige bei einer Kalichloricum-Vergiftung erhobene Blutbefunde, Med. Klin. **5**:1929, 1909.

blastic and monocytic leukemia,[10] relapsing fever,[11] pneumococcic and streptococcic sepsis [12] and endocarditis lenta,[13] and in experimental animals (rabbits following typhoid vaccination [14] and injection of cultures of Bacillus proteus [15] and colloidal dyes [16]). For a detailed review of these conditions, the reader is referred to Abt's excellent review.[3]

THE MONONUCLEAR PHAGOCYTIC CELLS

The cells which had ingested erythrocytes and nucleated red cells in the 3 cases here reported were all of the large monocytic type which Sabin [17] and other authors spoke of as the mononuclear phagocyte, endothelial leukocyte, or clasmatocyte. Larger than the normal monocyte, this cell has a light-staining, eccentric nucleus with a light cytoplasm which contains ingested matter in varying-sized vacuoles. The cell is actively phagocytic. This activity was aptly demonstrated by Rowley [7] in a case of severe secondary anemia in which she was able to demonstrate actual phagocytosis of erythrocytes by a large mononuclear cell in fresh blood droplets under the microscope.

The usual habitat of the mononuclear cell is in the tissues, and it makes its appearance in the circulating blood only in the conditions previously listed. The idea therefore arises that the clasmatocytes appear in the circulating blood only when an attempt is to be made to rid the blood of some noxious agent, which could be the blood cells themselves. One could therefore surmise that the appearance of mononuclear phagocytes in the circulating blood indicates trouble within the blood stream or the blood-forming organs, since it has been found only in diseases having a direct effect on the blood itself. It was suggested by Rowley [7] from her study of a case of severe secondary anemia that the production of the anemia might be due to the progressive phagocytosis of the erythrocytes by the mononuclear phagocytes. Is

10. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie, München. med. Wchnschr. **60**:1981, 1913.

11. Hung, S. L.: Ueber die Erythrophagozytose durch Monozyten und Lymphozyten im peripheren Blut bei Febris rekurrens und Malaria, Arch. f. Schiffs- u. Tropen-Hyg. **40**:17, 1936.

12. Wright, A. E.: Pneumococcic Sepsis, Brit. M. J. **1**:143, 1906. Kaznelson, P.: Seltene Zellformen des stromenden Blutes, Deutsches Arch. f. klin. Med. **128**:131, 1919.

13. Van Nuys, F.: An Extraordinary Blood: Presence of Atypical Phagocytic Cells, Boston M. & S. J. **156**:390, 1907.

14. Miller, T. G., and Pepper, O.: Phagocytosis of Erythrocytes, J. Immunol. **1**:383, 1916.

15. Dieckmann, H.: Histologische und experimentelle Untersuchungen über extramedulläre Blutbildung, Virchows Arch. f. path. Anat. **239**:451, 1922.

16. Simpson, M. E.: The Experimental Production of Macrophages in the Circulating Blood, J. M. Research **43**:77, 1922.

17. Sabin, F. R.: Bone Marrow, Physiol. Rev. **8**:191, 1928.

mononuclear erythrophagocytosis therefore the body's method of ridding itself of diseased red blood cells?

However, this question must for the present remain purely theoretic, since the phagocytic cells have not so far been found in large enough numbers in the blood stream to warrant the formation of any definite conclusions about the phenomenon.

It must be considered that this phenomenon may be due to an abnormal activity of the clasmatocytes resulting, for example, in the production of an anemia. No definite basis for this idea exists, since the phagocytes disappear as an anemia is corrected, and all of the cases in which the phenomenon has been found were instances of distinct disease entities, leading one to believe that the phenomenon is due to, rather than the cause of, the disease.

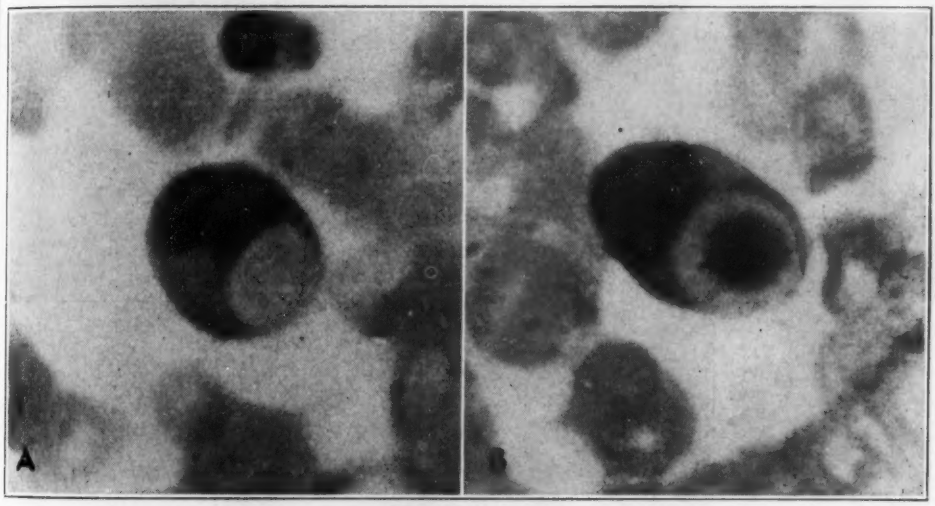

Fig. 1 (case 1).—*A*, blood smear (Wright stain) showing a phagocyte containing an erythrocyte. The erythrocyte was definitely pink staining. *B*, blood smear (Wright stain) showing a phagocyte containing a normoblastic nucleus surrounded by a definite clear, unstained zone.

The purpose of this paper is not to form any definite conclusions about mononuclear erythrophagocytosis but merely to suggest a few plausible ideas as to the reasons why one finds this phenomenon only in diseases having a direct effect on the blood or the blood-forming organs and to report 3 cases of acute hemolytic anemia of the newborn in which the phenomenon was observed.

REPORT OF CASES

CASE 1.—J. K., a boy, was delivered May 17, 1945, by cesarean section. This section was performed because hemolytic anemia of the newborn was suspected, since four previous pregnancies had terminated in stillborn infants with edema

and jaundice. This pregnancy was terminated at eight months. The father and baby were Rh positive, the mother was Rh negative. The infant was small, pale and slightly jaundiced. The liver and spleen were definitely enlarged, and a moderate degree of edema was present. Blood counts immediately after delivery revealed 1,300,000 red cells per cubic millimeter, with 80 per cent of the differential count being nucleated red cells. Studies of stained blood smears revealed erythrophagocytosis. The infant was given 50 cc. of concentrated blood cells one hour

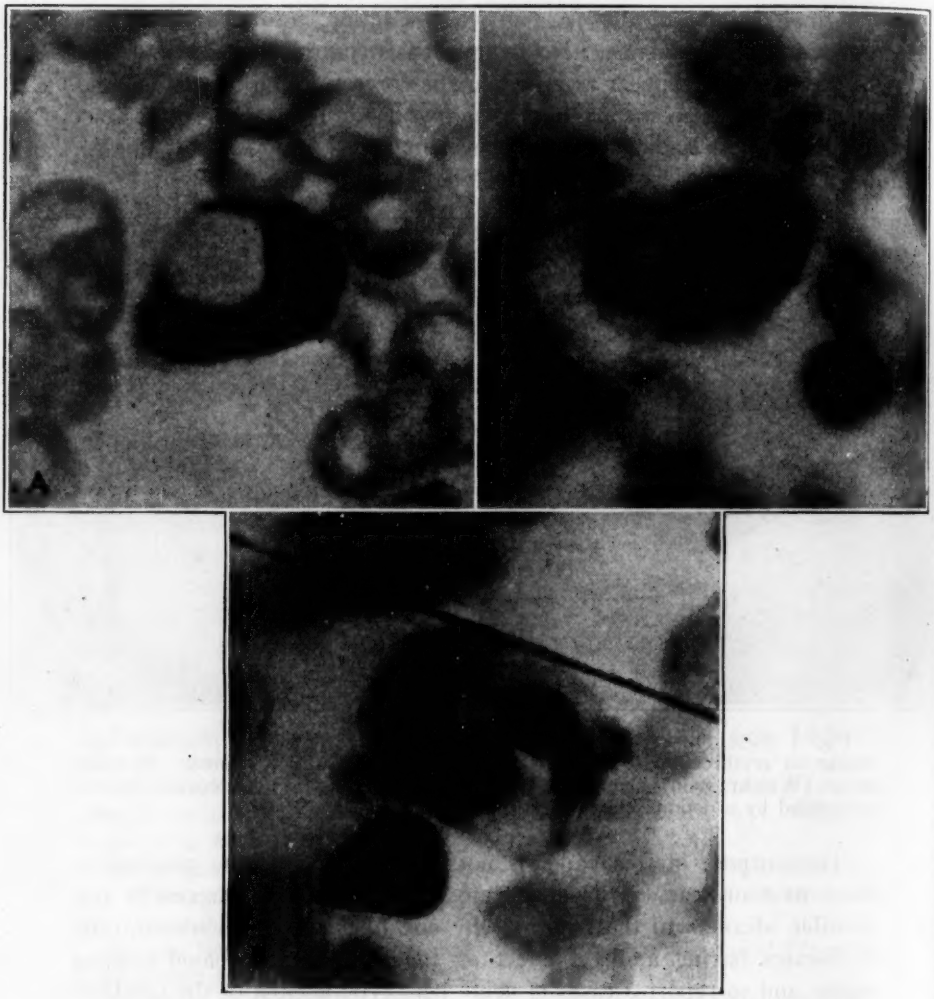

Fig. 2 (case 2).—*A*, blood smear (Wright stain) showing a phagocyte containing a definite erythrocyte; adjacent to the erythrocyte is a normoblastic nucleus showing no clear zone around it. *B*, blood smear (Wright stain) showing a large phagocytic cell with a large clear space in the cytoplasm in which are seen 3 dense-staining nuclei, one of which resembles closely a typical erythroblastic nucleus. *C*, blood smear (Wright stain) showing a phagocyte containing 2 adjacent pink-staining erythrocytes.

after delivery and again twelve hours after delivery. Edema and jaundice continued, and the erythrocyte count rose to 2,300,000. Twenty-four hours after birth the red cells numbered 1,500,000, wth 80 per cent nucleated cells. The infant died while preparations were being made for another transfusion.

Blood Smears.—Large numbers of nucleated red cells in all stages of development were found. Mononuclear cells resembling monocytes were observed which contained definite pink-staining erythrocytes. In others of these cells, large vacuoles, the size of an erythrocyte, were found; and occasionally a dark normoblastic nucleus was revealed in the cytoplasm of these monocytic cells.

Autopsy.—Generalized edema, with yellow serous fluid in all body cavities, was present. The liver and spleen were enlarged. Reports on the microscopic studies are not as yet available.

CASE 2.—T. L., a boy, was born at full term with a normal delivery, July 11, 1944. The infant was pale at birth and became jaundiced a few hours later.

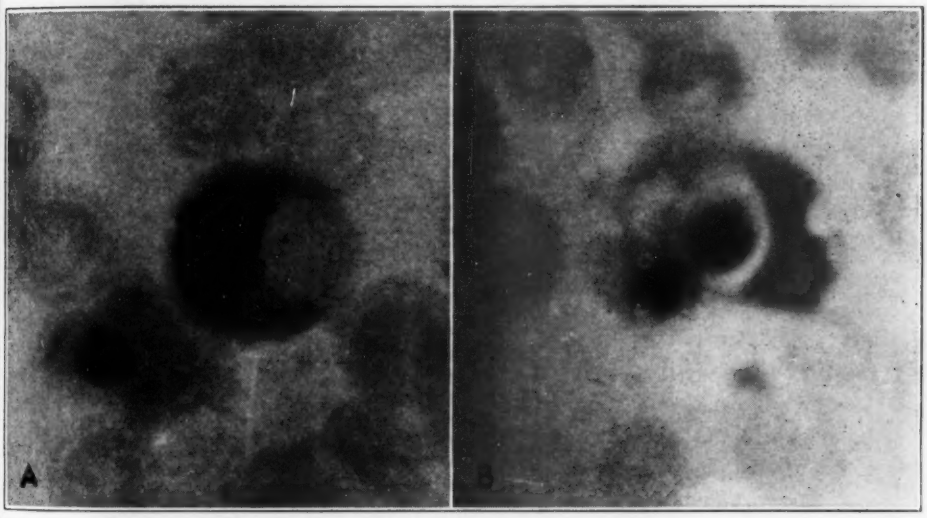

Fig. 3 (case 3).—*A,* blood smear (Wright stain) showing a very large monocytic cell containing a pink-staining erythrocyte. *B,* blood smear (Wright stain) showing a very large phagocytic cell containing a normoblastic nucleus surrounded by a clear unstained zone. Adjacent to this is a small pink-staining erythrocyte. A normoblast is seen lying at the edge of the mononuclear cell.

Pallor and jaundice were extreme twelve hours after delivery, and the liver and spleen were enlarged but no edema was present. Blood counts at that time revealed 2,000,000 red cells per cubic millimeter, with 95 per cent nucleated red cells. Fifty cubic centimeters of concentrated blood cells was given intravenously, and the count rose to 2,510,000, with 90 per cent nucleated red cells.

The birth of the patient was the result of the first pregnancy of the mother. Examination of the blood showed the mother to be Rh negative and the baby and father to be Rh positive. There was no family history of jaundice, edema or anemia of the newborn.

Progress.—The patient was given 50 cc. of concentrated blood cells daily for three days. The count rose to 4,550,000 erythrocytes, with 10 per cent nucleated red cells. Jaundice gradually subsided, and the liver and spleen decreased in size. Pallor was again noticeable on the tenth day of life, and the red cell count had dropped to 3,000,000 with 16 per cent normoblasts. Transfusions relieved the anemia. The infant is now 10 months old and is apparently healthy, with no anemia.

Blood Smears.—The same observations were made as in case 1, but the number of phagocytic cells was greater in this case.

CASE 3.—A. G., a girl, was delivered by cesarean section July 11, 1944, with spontaneous respiration and cry. The baby seemed normal in all respects until the sixth day, when it was noted that she seemed rather pale and slightly jaundiced. The next day the jaundice was pronounced but the liver and spleen were not enlarged. A red cell count showed 2,580,000 cells per cubic millimeter, with

Blood Counts in Three Cases of Erythrophagocytosis

Case	Days	R. B. C. per Cu.Mm.	Nucleated R. B. C. per 100 W. B. C.	Erythrophagocytes per Stained Slide
1	At birth	1,300,000	80	14
	½	2,300,000	72	10
	1	1,500,000	80	12
2	½	2,000,000	95	24
	1	2,500,000	90	20
	3	4,500,000	10	6
	4	3,220,000	4	2
	5	3,560,000	6	2
	6	3,720,000	3	2
	10	3,000,000	16	10
	14	4,680,000	0	0
3	3	4,870,000	0	0
	4	3,660,000	0	0
	5	3,500,000	0	0
	6	3,070,000	4	6
	7	2,580,000	8	8
	9	4,200,000	0	2
	13	4,400,000	0	0
	16	4,260,000	0	0

8 per cent nucleated red cells. Seventy cubic centimeters of bank blood was given intravenously, and her color improved.

The patient's birth was the result of the third pregnancy of a mother whose blood was Rh negative. The baby's and the father's blood were Rh positive. The first pregnancy resulted in the birth of a full term normal infant. The second pregnancy resulted in a miscarriage at six months.

Progress.—On the eighth day a transfusion of 50 cc. of concentrated cells was given. The jaundice did not increase. After transfusion, the red cell count rose to 4,200,000 per cubic millimeter and has remained within normal limits since. The infant is now 10 months old and seems healthy.

Blood Smears.—At no time was a great number of nucleated red cells found. The highest number observed was 8 per hundred white cells counted. The young red cells appeared at the height of the anemia and disappeared when the anemia was relieved. Phagocytes appeared when the nucleated red cells appeared and disappeared at approximately the same time as they did.

COMMENT

The mononuclear cells found containing pink-staining erythrocytes were of the monocytic type previously described. The phagocytic cells included in the table were those in which actual red cells which still retained their staining properties were present. In most blood smears examined, equal numbers of phagocytic cells were found which had in their cytoplasm vacuoles the size of an erythrocyte or smaller which were not stained. In a number of these cells, a dense-staining nucleus resembling that of a normoblast or small lymphocyte was found in the cytoplasm. In several instances this normoblastic nucleus was surrounded by a definite clear, nonstaining zone which gave the ingested cell the appearance of a normoblast. In one instance, a definite typical erythroblastic nucleus was found in the cytoplasm of a phagocyte.

Occasionally I was able to demonstrate 2 erythrocytes in the same cell. When 2 erythrocytes were found in a single cell, they were located adjacent to one another in some cells and at opposite poles of the cells in others.

It is interesting to note that the greatest numbers of phagocytes were found when the red cell count was the lowest and the nucleated red cell count was the highest. As the anemia was relieved by transfusions and as the nucleated red cells decreased, the phagocytic cells also decreased in number. In case 2 the phagocytic cells increased in number when a second drop in the red cell count occurred and the number of nucleated red cells rose. The nucleated red cells and the phagocytes again disappeared from the blood as the anemia was relieved by transfusion a second time.

In case 3, the phagocytes were not found until seven days after birth, at which time the red cell count had dropped to 3,000,000 and nucleated red cells had appeared in the blood. The phagocytes disappeared when anemia was relieved and did not reappear and were not present ten months after birth.

The number of phagocytic cells rose or fell in direct proportion to the rise or fall in the number of immature red cells, and the greatest number of phagocytes was observed in the cases in which there was the greatest number of immature cells. This was brought out also in Abt's case [3] and in Wyatt, Cooper and Groat's cases.[4] A question is therefore raised as to why one finds a large number of phagocytic cells in anemias of the newborn manifesting a decided bone marrow response, and few phagocytes in those showing a slight bone marrow response, since the phagocytic cells are believed to be formed from the endothelial cells lining the capillaries and not in the bone marrow. On the other hand, if the cells are true monocytes and not clasmatocytes, one would expect them to be present in numbers proportionate to the bone marrow response.

SUMMARY

Three cases of hemolytic anemia of the newborn in which mononuclear erythrophagocytosis was observed are added to those already reported in the literature.

In all the cases definite evidence of phagocytosis of erythrocytes was found.

Points of speculative interest about this phenomenon are presented in an attempt to clarify the position of the erythrophagocytes in the blood in cases of diseases having a direct effect on the blood or blood-forming organs.

A possible role of the phagocytic mononuclear cells is suggested.

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TYPHOID EMPYEMA

Report of a Case with Recovery

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AND
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OF THE many complications of typhoid, typhoid empyema is one of the rarest. Holt [1] (1939) failed to mention typhoid empyema as a complication of typhoid, and Brennemann [2] (1944) said, "Pleurisy and empyema may develop as a complication of any variety of pneumonia, though primary pleurisy is rare."

Owing to the rarity of this complication and the fact that the complaints on admission were referable to the chest, this case is being reported.

REPORT OF CASE

R. D., a 12 year old white girl, was admitted to the Children's Free Hospital on June 24, 1942, from Gratz, Ky., with the chief complaints of "chills, fever, loss of weight and the coughing up of blood." According to the parents, the child was perfectly well until twenty-four days prior to admission, at which time she felt weak and fainted. The following day fever, chills and vomiting developed, which persisted to the time of admission. Two weeks after the onset of the present illness, her stools became diarrheal in character, and three days prior to admission they contained blood. Four days before admission, she had a severe pain in the right side of the chest accompanied with hemoptysis.

Shortly before the onset of the illness, she and the remainder of the family had been visiting in the "mountains."

She had been immunized for smallpox, typhoid and diphtheria. The family history was noncontributory.

Physical examination at the time of admission revealed an acutely ill child, crying from pain in the right side of her chest. The lips were parched, and the skin was hot and dry. There was a definite lag on the right side of the chest, and the percussion note was impaired posteriorly, especially below the level of the second rib. Over this area breath sounds were diminished and tactile fremitus was absent. Except for mild abdominal distention, the remainder of the physical

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From the Department of Pediatrics, University of Louisville School of Medicine.

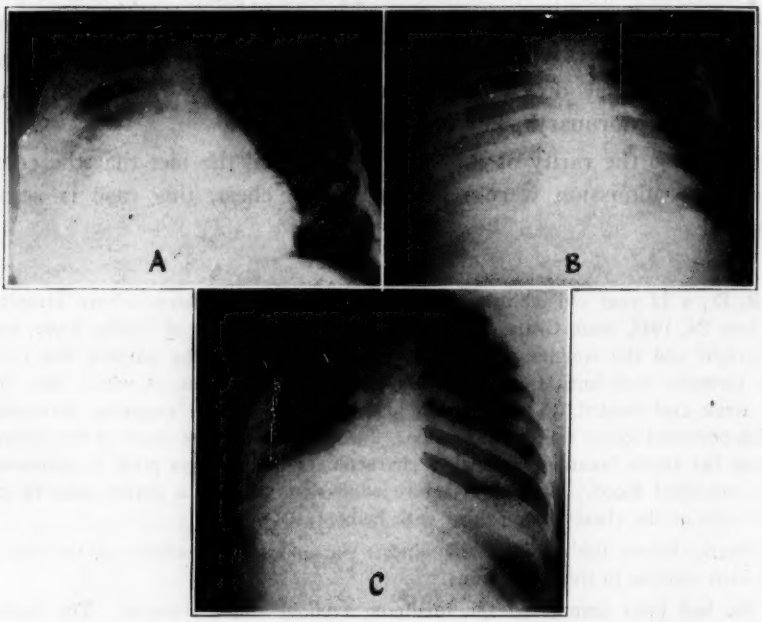
1. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, ed. 11, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1939.

2. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 2, chap. 30, p. 6.

examination gave no remarkable results. The temperature was 102.4 F., with a pulse rate of 112 beats per minute and respiration rate of 30 per minute.

The red blood cell count was 5,010,000 per cubic millimeter, with a hemoglobin level of 97.4 per cent and a white blood cell count of 17,200 per cubic millimeter, with polymorphonuclear leukocytes 57 per cent, lymphocytes 27 per cent, monocytes 2 per cent and stab forms 14 per cent. The urinalysis revealed albumin (1 plus) and 5 to 15 white blood cells per field. A roentgenogram of the chest showed a homogeneous density in the base of the right lung (fig. *A*).[3]

Aspiration of the chest revealed a very small amount of thick, bloody material from which Bacterium typhosum[4] was isolated on culture. On June 26 and 29, her blood serum agglutinated Bact. typhosum, in a dilution of 1 to 1,280, but cultures of the whole blood were negative for the organism.



A, roentgenogram of the chest of R. D. revealing a homogeneous density in the base on the right side. *B*, roentgenogram revealing an accumulation of fluid in the right pleural cavity. *C*, roentgenogram showing an area of increased density in the right lung.

The patient was given a high vitamin caloric fluid diet, supplemented by infusions of dextrose and isotonic solutions of sodium chloride. Although she had considerable sedation, she continued to have hemoptysis and vomiting.

The fever was continuous, and at times the temperature reached 105 F.

In spite of repeated transfusions, her red blood cell count on July 1 had dropped to 3,350,000 per cubic millimeter with a hemoglobin level of 71 per cent. Also, at this time, a culture of her urine showed Bact. typhosum.

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3. Prepared and interpreted by Dr. H. L. Townsend.

4. Dr. J. A. Kennedy, Director, Bacteriologic and Serologic Laboratories, Louisville General Hospital.

Thoracentesis was repeated July 2, and 5 cc. of foul chocolate-colored material was aspirated which on culture showed no growth; however, for the first time, culture of her stool was positive for Bact. typhosum.

On July 3, her stool, her sputum and the fluid aspirated from the chest all proved to contain Bact. typhosum, but the culture of the blood still showed no growth.

On July 6, thoracentesis was again repeated and yielded 250 cc. of purulent, gaseous, chocolate-colored material with a fecal odor. Owing to a peristent cough, it was felt that a bronchopleural fistula had developed, and the procedure was terminated before all the material possible could be aspirated. Bact. typhosum was again isolated on culture from this material.

On July 7 she was transferred to a private hospital. Her red blood cell count at the time of admission was 3,430,000 per cubic millimeter with a hemoglobin level of 61.6 per cent and a white blood cell count of 7,100 per cubic millimeter, with polymorphonuclear leukocytes 70 per cent, lymphocytes 29 per cent and basophils 1 per cent. The diet for patients with typhoid was continued, and an additional transfusion of 250 cc. of citrated whole blood was given. A second roentgenogram (fig. *B*), revealed an accumulation of fluid in the right pleural cavity.

On July 8 thoracentesis of the right pleural space produced 500 cc. of chocolate-colored material, but the procedure was again terminated because of the persistent cough. Another roentgenogram of the chest still showed considerable fluid remaining in the right pleural cavity.

On July 10 another pleural aspiration was done, and 350 cc. of the same type of material was aspirated. Owing to the persistent accumulation of the fluid in the pleural cavity it was decided to do an open drainage. On July 13, with the patient under ether anesthesia, a thoracotomy [5] of the eighth rib was done in the posterior axillary line, and 500 cc. of brownish material was obtained. A bronchopleural fistula was demonstrated at the time of operation. A soft rubber catheter was inserted for drainage. Following the operation the child's course was stormy, and her condition appeared extremely toxic. At one time she seemed near death, but she was revived by aspiration of a considerable amount of mucus and pus from the trachea. Postoperative treatment consisted of infusions of dextrose and isotonic solutions of sodium chloride and transfusions of whole blood and plasma.

Another roentgenogram of the chest, on July 14 (fig. 1, *C*), revealed in addition to the surgically drained empyema an area of decreased density in the right lung suggestive of destruction.

In spite of a daily rise in temperature for the next two weeks and continued drainage from her surgical wound, she had a gradual improvement.

A roentgenogram on July 31, revealed a small amount of fluid in the right thoracic cavity and an increased density in the base of the right lung suggesting an atelectasis.

From August 2 until the time of her discharge, August 14, she was afebrile and the wound ceased to drain.

She has been followed to date, and no recurrence of typhoid empyema has been revealed either by clinical or by roentgenographic observation.

SUMMARY

A case of typhoid in a child, complicated by typhoid empyema, with recovery is reported.

5. Performed by Dr. Lawrence W. Nehil.

Progress in Pediatrics

CORONARY OCCLUSIVE DISEASE IN INFANTS AND IN CHILDREN

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THE age at which coronary occlusive disease is of importance in differential diagnosis has been lowered steadily as knowledge of that disease has increased. Previously considered a disease of middle-aged or elderly persons, and so described in most of the standard text-books, occluding coronary lesions are fairly frequent in young adults, as shown by the recent report of French and Dock.[1] These authors reviewed the findings in 80 cases of fatal coronary arteriosclerosis in young soldiers. Five of the patients were in the group from 20 to 22 years and 9 in the group from 23 to 25 years. The lesion present in every case was arteriosclerosis of the same atheromatous type as commonly found in older persons. Weinstein[2] has recently shown that coronary disease, by him called "atypical" because of its origin, may appear also in young persons as a feature of rheumatic fever, either in the acute phase or in an acute exacerbation. His observations, likewise, were made on men in military service.

The importance and nature of coronary occlusive disease in a still younger age group, that of infants and children, have not been fully appreciated. Obliteration or partial occlusion of the main or smaller coronary stems can appear at any age and has been encountered even in stillborn infants. The standard texts of medicine, pediatrics and pathology give at most only a general statement of the possibility of this lesion in infants and children, and many do not mention such coronary lesions.

One great difference can be noted between the lesions of coronary arteries occurring in adults and those occurring in infants and children. In adults a great majority are related to arteriosclerotic disease of the atheromatous type, with proportionately few being due to other processes. In infants and children, however, that type of arteriosclerosis is a relatively rare factor in causing occlusion, and thus the

From the Department of Pathology, University of Michigan.

1. French, A. J., and Dock, W.: Fatal Coronary Arteriosclerosis in Young Soldiers, J. A. M. A. **124**:1233-1237 (April 29) 1944.

2. Weinstein, J.: "Atypical" Coronary Disease in Young People, Ann. Int. Med. **21**:252-271 (Aug.) 1944.

significance of other types is increased. The lesions which may produce partial or complete occlusion include:

I. Medial calcification with fibroblastic proliferation of the intima
II. Polyarteritis (periarteritis) nodosa
III. Arteriosclerosis (atherosclerosis)
IV. Syphilitic arteritis
V. Embolism
VI. Congenital abnormalities
VII. Rheumatic arteritis
VIII. Hypertension

None of these processes is limited to infants and children, but some of them are rarely found in adults. The only cause of coronary occlusive disease in adults that has not been described in any person below the age of 17 years is thromboangiitis obliterans (Buerger's disease).

In the department of pathology of the University of Michigan, tissues have been examined from 9 infants or children under the age of 17 years in whom occlusion of one or more coronary arteries was an important feature. The cases of these patients are included in the following report. In addition, there is reported 1 case from another institution which illustrates a process not observed in the series of autopsies performed in this department.

I. MEDIAL CALCIFICATION WITH FIBROBLASTIC PROLIFERATION OF THE INTIMA

Fibroblastic proliferation of the intima of the coronary arteries in infants has frequently been found associated with calcification of the media of the vessel. The process may be sufficiently severe to decrease the lumen of the vessel or to occlude it completely. This arterial lesion has recently been discussed by Brown and Richter,[3] who designated the process as "medial coronary sclerosis." These authors summarized 6 cases that had been reported previously[4] and

3. Brown, C. E., and Richter, I. M.: Medial Coronary Sclerosis in Infancy, Arch. Path. **31**:449-457 (April) 1941.

4. (*a*) Bryant, J. H., and White, W. H.: A Case of Calcification of the Arteries and Obliterative Endarteritis, Associated with Hydronephrosis in a Child Aged 6 Months, Guy's Hosp. Rep. **55**:17-28, 1891. (*b*) Surbek, K.: Ueber einen Fall von kongenitaler Verkalkung, mit vorwiegender Beteiligung der Arterien, Centralbl. f. allg. Path. u. path. Anat. **28**:25-39, 1917. (*c*) Hughes, F. W. T., and Perry, C. B.: Senile Arterial Changes in a Child Aged 7 Weeks, Bristol Med.-Chir. J. **46**:219-222, 1929. (*d*) Forrer, H.: Ausgedehnte Gefässverkalkung im frühen Kindesalter, Inaug. Dissert., Zurich, J. H. Meier, 1930. (*e*) Iff, W.: Über angeborene Verkalkungen, besonders der Arterien, Virchows Arch. f. path. Anat. **281**:377-395, 1931. (*f*) Lightwood, R.: A Case of Dwarfism and Calcinosis Associated with Widespread Arterial Degeneration, Arch. Dis. Childhood **7**:193-208 (Aug.) 1932.

added 1 of their own. In addition to these 7 cases, reports of 8 others are available [5] in the literature, 5 of which have been published since Brown and Richter's report. The ages of the 15 patients ranged from 1 day to 27 months. Seven were boys and 8 girls. In all cases other arteries in addition to the coronary arteries were involved, although the process in the latter was frequently most pronounced and of major importance to the patient. Five of the children had died suddenly, while others had given clinical evidence of cardiac failure.

In 4 of the cases in my material there were lesions considered to belong to this type. Although the coronary arteries were involved in all cases, in only 1 was the lesion severe enough to be the probable cause of death. In 2 other cases it was a possible contributing cause, while in a fourth case only earlier stages of the process were shown. The detailed clinical courses in these 4 cases and the gross and microscopic observations at the autopsies are described elsewhere,[6] together with a consideration of the possible etiologic factors in these and the 15 cases previously reported.

The infant in whom the lesion of the coronary artery was the cause of death (case 1) was 3 months old. His illness had lasted only three days and was thought to be "influenzal pneumonia." At autopsy one coronary artery showed calcification of the media and fibroblastic proliferation of the intima, with complete occlusion of the lumen of the artery except for small foci of recanalization. Other coronary arteries showed a similar but less pronounced process. Small areas of recent infarction were present in the myocardium. Arterial changes similar to those in the coronary arteries were found in pulmonary and splenic arteries.

In 2 of the other cases (cases 2 and 3) the patients were aged 2 months and 6 months; the fourth case was that of a stillborn fetus. Two of the patients were boys. All 3 infants showed focal calcification of the media of a main coronary artery with fibroblastic proliferation of the adjacent intima. In the 2 infants who had lived, this prolifera-

5. (*a*) Verocay, J.: Arterienverkalkung bei angeborener Lues, Frankfurt. Ztschr. f. Path. **24**:109-136, 1920. (*b*) Oppenheimer, E. H.: Partial Atresia of the Main Branches of the Pulmonary Artery Occurring in Infancy and Accompanied by Calcification of the Pulmonary Artery and Aorta, Bull. Johns Hopkins Hosp. **63**:261-277 (Oct.) 1938. (*c*) van Creveld, S.: Coronary Calcification and Thrombosis in an Infant, Ann. pædiat. **157**:84-92 (Aug.) 1941. (*d*) Baggenstoss, A. H., and Keith, H. M.: Calcification of the Arteries of an Infant, J. Pediat. **18**:95-102 (Jan.) 1941. (*e*) Anderson, D. H., and Schlesinger, E. R.: Renal Hyperparathyroidism with Calcification of the Arteries in Infancy, Am. J. Dis. Child. **63**:102-125 (Jan.) 1942.

6. Stryker, W. A.: Calcification of Arteries in Infancy, Am. J. Path., to be published.

tion of the intima had caused a slight reduction in the lumens of the arteries. In all 3 infants other arteries in addition to the coronary arteries were involved to a varying degree.

The causes of this lesion are not known. In some instances severe renal lesions are present, and in these cases the arterial lesions may represent metastatic calcification secondary to an altered calcium-phosphorus ratio in the blood. Similar lesions are sometimes found in "renal rickets" (renal osteodystrophy). Altered calcium-phosphorus ratios likewise occur in primary parathyroid hyperplasia and in primary or destructive osseous disease, and thus these conditions also may be etiologic factors. Calcification of arteries has occasionally been observed following an intake of excessive amounts of vitamin D.[7] Other possible causal factors that have been considered include pyogenic infection, syphilis and allergy. None of these, however, is present in all cases of medial calcification, and thus no one of them can be accepted as the sole cause. The most attractive hypothesis is that in all cases an embryonally weak protoplasm is present in these infants, and on this poor ground substance any one of many factors may act as a precipitating mechanism. Such a weakness of the protoplasm has been postulated [8] as a factor in arteriosclerosis of the adult type and may be equally a factor in the infantile type.

II. POLYARTERITIS (PERIARTERITIS) NODOSA

The clinical symptoms of polyarteritis (periarteritis) nodosa vary according to the tissue in which the vascular lesions are most severe or are most effectively placed. Among the clinical types of the disease, determined by the presenting symptoms, is the cardiac type, in which the coronary arteries are involved and in which the consequent myocardial lesions may be a cause of death. Polyarteritis nodosa may occur at any age; in 1931 Rothstein and Welt [9] discussed 21 cases of the disease which had been reported as occurring in infants and children up to the age of 15 years, and they added 2 new cases. In 17 of these 23 cases, there was involvement of the coronary arteries. In some of these, thrombosis of the affected vessel had resulted in occlusion of the lumen. Since that report, additional cases of the disease in this younger age group have been described.[10]

7. Reed, C. I.; Struck, H. C., and Steck, I. E.: Vitamin D, Chicago, University of Chicago Press, 1939.

8. Wells, H. G.: The Chemistry of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis—A Survey of the Problem, New York, The Macmillan Company, 1933, p. 324.

9. Rothstein, J., and Welt, S.: Periarteritis Nodosa in Infancy and in Childhood, Am. J. Dis. Child. **45**:1277-1308 (June) 1933.

(Footnotes continued on next page)

The characteristic lesions of the vessels in the acute phase of polyarteritis nodosa make possible a definite diagnosis. The identity of the lesions in cases of chronic or healed polyarteritis is not so certain, and thus the relationship of certain vascular changes to the more definite acute disease has not as yet been demonstrated completely. Arkin,[11] in 1930, published a clinical and pathologic study of 5 cases; 1 of these he considered to be an instance of the healed lesion. He asserted that the essential changes of this stage are replacement of the wall, especially the inner media, including the elastica interna, by fibrous scar tissue, reduction of the lumen of the vessel both by proliferation of subendothelial connective tissue and by organization of thrombi and periarterial fibrosis. Associated with these vascular lesions may be infarcts or atrophy of the organs supplied. Other descriptions of the healed lesions have been given by Weir[12] and by Vance and Graham[13]; the latter expressed the belief that the healed state may show only the intimal proliferation without changes in the media.

In 1 of the cases in my series, the typical lesions of acute polyarteritis nodosa were revealed at autopsy, and thus it is included here. In addition, other vessels showed changes which may be of importance in determining the lesion of the healed stage of the disease.

CASE 5.—A 15 year old boy had complained of attacks of severe headache for one year. Five years prior to the onset of this symptom he had had hematuria, the exact duration of which was not known. Seven weeks before admission to the hospital he noted failing vision. There had been occasional sharp shooting pains in the chest; two weeks before admission he had complained of abdominal pain, and appendicitis was suspected. During his hospitalization a diagnosis of subacute nephritis was made. His blood pressure was 210 systolic and 160 diastolic; a Wassermann test of the blood elicited a negative reaction. He appeared to respond well to treatment and was about to be discharged from the hospital when he suddenly died.

At autopsy the heart was hypertrophied. Involving the anterior descending branch of the left coronary artery was a globular swelling 3 mm. in diameter; section of this showed the lumen to be nearly obliterated. No gross abnormalities of the other coronary arteries were noted. On microscopic examination of the heart, a large coronary stem showed acute fibrinoid degeneration and necrosis of

10. (*a*) Keith, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, J. Pediat. **18**:494-503 (April) 1941. (*b*) Coe, M.; Reisman, H. A., and DeHoff, J.: Periarteritis Nodosa in a Nine-Year-Old Child, ibid. **18**:793-798 (June) 1941.

11. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa: A Report of Five Cases, One Histologically Healed, Am. J. Path. **6**:401-426 (July) 1930.

12. Weir, D. R.: Polyarteritis Nodosa: Report of a Case, Am. J. Path. **15**: 79-88 (Jan.) 1939.

13. Vance, B. M., and Graham, J. E.: Periarteritis Nodosa Complicated by Fatal Intrapericardial Hemorrhage, Arch. Path. **12**:521-532 (Oct.) 1931.

the wall, with disruption of the media and the formation of an aneurysm (fig. 1). There was occlusion of the lumen by the inflammatory process. The lesion was typical of those seen in acute polyarteritis nodosa. A similar process was seen in another area; here the media was intact along one side of the vessel but was entirely absent on the opposite side where an aneurysm had formed.

The vessel which had been seen grossly to be nearly occluded did not show these acute lesions on microscopic study. Both the intima and the media were replaced by a young fibroblastic connective tissue, and the proliferation of this tissue into the lumen had resulted in the partial occlusion. In sections stained for elastic tissue (Verhoeff stain), no internal elastic lamina could be found, and

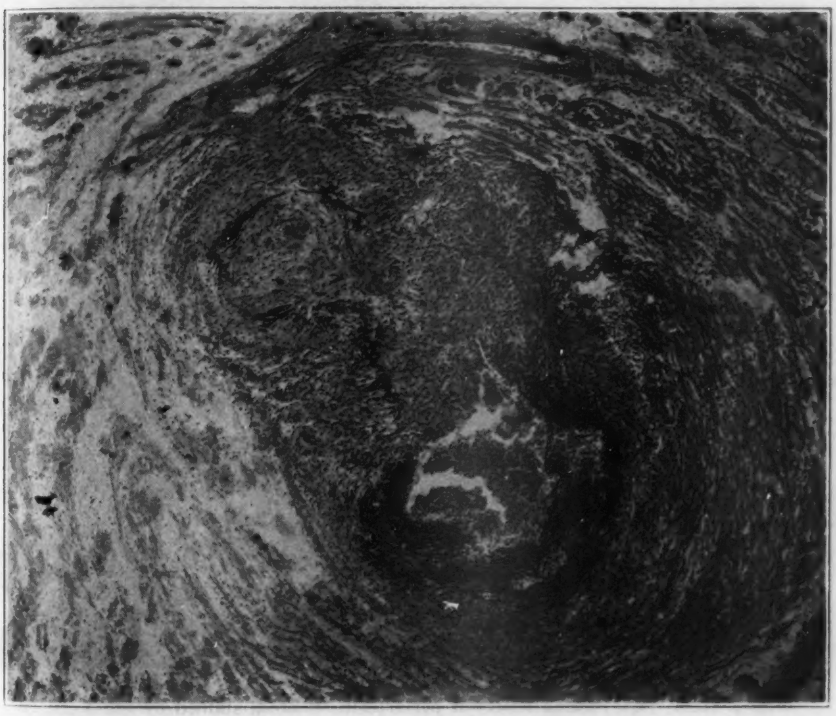

Fig. 1 (case 5).—Acute lesion of polyarteritis nodosa (periarteritis nodosa), with fibrinoid necrosis of wall and aneurysm formation. × 46.

only a few fragments of elastic tissue could be identified in the outer media (fig. 2). There was a perivascular mantle of collagenous connective tissue. This appearance is like that described by Arkin [11] for the healed stage of polyarteritis nodosa.

In another coronary artery a small mural thrombus was found. The walls of this vessel were normal. Still another coronary artery showed a moderate fibrosis of the intima with areas of vacuolation; this lesion was like the juvenile arteriosclerosis frequently seen in children dying of infectious disease.

No lesions were found in the myocardium. The kidneys showed a moderate subacute glomerulotubular nephritis; some of the larger arterioles showed a non-

occlusive intimal proliferation, while smaller branches showed hyalinization of the entire wall. Other vessels (cerebral arteries, aorta) showed only slight intimal proliferation with no medial lesions.

A variety of symptoms, as exhibited by this patient, is frequently the clinical picture of polyarteritis nodosa and is usually due to vascular lesions in multiple organs. The autopsy in this case, however, showed typical lesions only in the heart, and thus this is a comparatively localized form of polyarteritis nodosa. The possibility of such localized

Fig. 2 (case 5).—Healed lesion of periarteritis nodosa, stained by the Verhoeff method for elastic tissue. Only a few fibers of elastic tissue are visible. Compare with the well marked internal elastic lamina in the small branch at the lower right hand corner. × 53.

involvement has previously been discussed. The identity of the disease is shown without question by the presence of the active lesions.

Case 6.[14]—Another case in the present autopsy series is of interest here because it also may represent an instance of localized polyarteritis nodosa limited to the coronary and splenic arteries. There were no acute lesions in this second case, and its right to inclusion in this group is not as well established as is that of the first example.

14. The abstract of the clinical history was furnished by Dr. Fred Palmer, of the department of pediatrics, University of Michigan Medical School.

A girl, 11 years old at the time of her death, had been under observation for six years. Routine roentgenologic examination of her chest at the age of 5 years suggested a moderate cardiac enlargement; at 10 years the blood pressure was found to be 152 systolic and 125 diastolic. Because of gross hematuria, albuminuria and the presence of urinary casts, a diagnosis of chronic hemorrhagic nephritis was made. An electrocardiogram three months later was reported as showing "moderate right axis deviation with rather large P waves," suggesting "mitral stenosis." Hypertensive retinopathy, grade III, was present also at this time.

Seven months before death the patient was admitted to the hospital, with signs of cardiac decompensation. The heart sounds were of poor quality, with a split second sound. Blood pressure was 138 systolic and 100 diastolic. There were generalized edema and an enlarged liver. Four days after admission the child complained of pain in both axillas. The next day she appeared to be in shock and complained of a severe generalized abdominal pain. Cyanosis was present. The pulse was thready, and there was a gallop rhythm. Rapid digitalization was effected. An electrocardiogram now showed definite right axis deviation, suggesting right ventricular enlargement. Mild elevations of temperature were frequent; a search for a focus of infection was unsuccessful. The patient went into shock and died in what appeared to be acute congestive heart failure.

The reaction to the Kahn test had been negative on two occasions. Chemical studies of the blood showed elevation of the nonprotein nitrogen to a maximum of 92 mg. per hundred cubic centimeters during the periods of decompensation, but the value one day before death was only 30 mg. Multiple urinalyses were essentially as originally reported. Studies of the blood showed mild hypochromic anemia and recurrent leukocytosis.

The family history was pertinent. The father was known to have had syphilis of the central nervous system more than a year before the patient's birth. Dementia paralytica later developed, and at autopsy chronic syphilitic aortitis was revealed. The mother died of heart failure (type unknown) at the age of 38; the maternal grandparents also died of cardiac failure, and 12 aunts and uncles on the maternal side were said to have hypertension.

At autopsy, the heart weighed 570 Gm. About half of its anterior surface was composed of left ventricle. The myocardium of the left ventricle was 12 mm. in thickness; near the apex the tissue was gray-white. Adherent to the endocardium over this area was a firm, friable, gray-white thrombus. The coronary arteries were normal in origin and distribution. The anterior descending branches and the circumflex branches of the left coronary artery showed slight thickening of their walls. There was complete occlusion of the terminal 2 cm. of the posterior descending branch of the right coronary artery by a firm hyaline gray-white material. This area of occlusion was adjacent to the infarct at the apex of the left ventricle. The lower lobe of the left lung contained a small hemorrhagic infarct; small infarcts were found also in the spleen, and the liver showed an acute exacerbation of chronic passive congestion.

On microscopic examination, the area of occlusion of the right coronary artery showed an extreme proliferation of the intimal connective tissue completely obliterating the lumen (fig. 3). In this tissue there were four small endothelium-lined spaces which appeared to be newly formed vessels. The internal elastic lamina could not be recognized with certainty with the routine hematoxylin and eosin stain, although small fragments of eosinophilic tissue resembling it were present. The demarcation of the intimal connective tissue from the media was sharp except at one point, where it extended through an area in which the media was interrupted. This region was interpreted as an aneurysm with obliterated lumen.

The media and adventitia were free from inflammatory infiltrations; there was a moderate proliferation of perivascular connective tissue. Sections through other portions of the right coronary artery and through other coronary branches showed proliferation of the intima varying in amount; in some places only a crescentic lumen remained, while elsewhere the proliferation was limited to one side of the artery or encircled the lumen but was less in amount. No other lesions of the media were seen. A Verhoeff stain for elastic tissue showed occasional small interruptions of the continuity of the internal elastic membrane and in some areas an appearance of reduplication. Because of the paternal history of syphilis, a search for spirochetes was made, although the lesions were not typical of that

Fig. 3 (case 6).—Healed periarteritis nodosa (?). This is the occluded artery. The disruption of the media at one point can be noted. × 67.

disease. No organisms were found in sections stained with the Warthin-Starry stain.

The gray-white tissue in the myocardium was an organizing infarct in which the replacement of the necrotic muscle by granulation tissue was nearly complete. The myocardium elsewhere showed a diffuse interstitial fibrosis. Remaining fibers were hypertrophied. There was proliferation of the subendocardial connective tissue, and on the endocardial surface of the area of infarction was the organizing mural thrombus previously described.

The infarct in the spleen had no unusual features, but two arteries near its margin showed moderate intimal proliferation. There was decided redundancy of the internal elastic lamina, which also showed areas of fragmentation and of

interruption of continuity. With the Van Gieson stain the elastica stained a dirty yellow-green instead of the usual bright yellow. The media and adventitia of these vessels were normal. Smaller vessels about the infarct contained organizing thrombi or emboli. The kidneys contained small subcapsular arteriolosclerotic scars, but no definite lesions of the vessels were noted. In the cerebellum was an area of anemic infarction. The intima of the aorta showed pronounced recent proliferation of connective tissue without degenerative changes. A similar but less pronounced change was seen in the pulmonary artery. The lungs, liver and spleen showed an acute exacerbation of chronic passive congestion.

The pathologic diagnoses were: obliterating endarterial proliferation of the coronary arteries, most pronounced in the terminal portion of the posterior descending branch of the right coronary artery; healed localized polyarteritis nodosa (?); extensive organizing myocardial infarcts; organizing mural thrombus in the left ventricle; cardiac hypertrophy; "hypertension"; organizing infarcts in the spleen with endarterial proliferation in adjacent arteries; recent thrombus or embolus in a pulmonary artery with hemorrhagic infarction of the lung; ischemic necrosis of the cerebellum; acute exacerbation of chronic passive congestion of the lungs, liver and spleen; decided intimal fibroblastic proliferation in the aorta and pulmonary artery; slight arteriosclerotic nephropathy; hydrothorax, hydropericardium, ascites and generalized anasarca, and lipidosis of the liver and the kidneys.

The diagnosis of healed polyarteritis nodosa in this case is based mainly on the interruption of the media in the one coronary vessel with the formation of an aneurysmal structure filled with young connective tissue. Unfortunately, stains for elastic tissue could not be performed on this vessel since the block containing it had been used for other purposes; these might have given assistance in the diagnosis. No abnormalities in the elastic tissue of the media of the other arteries were observed. The lesions of these arteries, even without medial damage, were comparable to those described by Vance and Graham.[18] If this is not an example of polyarteritis nodosa, the classification of the arterial lesions in this case is uncertain.

In 1929 McMichael[15] described an 18 month old child whose death followed thrombosis of the superior mesenteric artery. The descending branch of the left coronary artery and the other arteries of similar size showed a great proliferation of the connective tissue internal to the internal elastic lamina; the media and adventitia were normal. Thrombosis also was present in some of the vessels. There was fibrosis of the myocardium and infarcts in the spleen and kidneys. McMichael called the process "endarteritis obliterans" and excluded periarteritis nodosa by the absence of involvement of the adventitia. The term "endarteritis" is faulty since it implies an inflammatory process; a preferable term for the condition present in the arteries in McMichael's case and possibly in my case would be "obliterating endarterial pro-

15. McMichael, J.: Extensive Visceral Endarteritis Obliterans in a Young Child, Arch. Dis. Childhood **4**:165-169 (Aug.) 1929.

liferation," which merely describes the process without any reference to possible causation. This report by McMichael is the only one describing this lesion in a child; Perla and Seligman [16] have observed similar changes in the arteries of a woman 47 years old.

In the proliferation of the intima seen in infectious diseases [17] there is usually some inflammatory infiltration in the vessel wall and the primary cause is known. Likewise, in the hypertension of advanced renal disease intimal proliferation may occur, but the lesion of the kidney reveals the cause. In syphilis a proliferation of the intima may occur; this is often the chief lesion found in the smaller vessels and is responsible for much of the symptomatology of the disease. Syphilis as a possible etiologic factor must be considered in both the case presented here and in the one reported by Perla and Seligman.[16] In the latter a 4 plus Wassermann reaction was obtained from the patient's serum, and in the present case the father of the child was known to have had a syphilitic infection at least a year before the birth of the patient; the patient's reaction to the Kahn test, however, was negative on the two occasions that it was determined. McMichael [15] also considered the possibility of the process in his case being due to hereditary syphilis, but the Wassermann reactions of both the father and the mother were negative. In syphilis of the arteries, as in other infections, there is an associated inflammatory infiltration of the adventitia and possibly also of the media. This was lacking in all these cases. Likewise, there were no lesions suggestive of syphilis in the other viscera, and search for spirochetes in McMichael's case and in the present case was unsuccessful.

The possibility of a toxic or metabolic cause was considered by Perla and Seligman.[16] In their case, as in McMichael's,[15] an infection was present during the clinical course, and similarly in my case there were repeated infections of the upper respiratory tract, and an elevated temperature was a recurrent feature of the clinical picture. The relation between these infections and the vascular lesions remains problematic and theoretic. The same statement is true regarding metabolic factors.

III. ARTERIOSCLEROSIS (ATHEROSCLEROSIS)

It is remarkable that arteriosclerosis of the type usually found in adults, characterized by lipid deposits and fibrosis of the intima with frequently associated medial lesions, should be so rare a cause of coronary occlusive disease in persons below the age of 17 years.

16. Perla, D., and Seligman, B.: Diffuse, Obliterating Endarteritis of Unknown Etiology, Arch. Path. **7**:55-62 (Jan.) 1929.

17. The term "endarteritis" was first used by Friedländer (Friedländer, C.: Ueber Arteritis obliterans, Centralbl. f. d. med. Wissensch. **14**:65, 1876) to describe this process.

Deposits of lipids in the intima of the aorta and of the arteries are frequently seen in children, especially in those dying of infectious disease or of juvenile diabetes, but the process apparently does not become sufficiently pronounced to be of clinical importance.

In the reported cases of death due to coronary arteriosclerosis in childhood, the age of the youngest patient was 10 years. This case was described by Jokl and Greenstein.[18] A 10 year old boy died three minutes after participating in a boxing match; during the progress of the contest he had not appeared unduly distressed. "At autopsy the left descending branch of the coronary artery was blocked for a distance of about an inch, beginning ½ inch from the orifice. Above and below the occlusion were slight atheromatous changes in the intima." Histologic examination revealed an almost complete occlusion by a thickened and hyalinized intima and an organized thrombus. Deposits of calcium were seen between the intima and media; surrounding tissues showed infiltration by erythrocytes. The internal elastic lamina was disrupted. No other abnormalities of the arterial system were observed.

Benda [19] has reported the sudden death of a girl 13 years old. Autopsy revealed atherosclerosis of the aorta and large arteries, including the left coronary artery, in which there was obliteration of the anterior descending branch. There was an infarct of the myocardium with rupture of a resulting ventricular aneurysm. The kidneys showed advanced arteriolosclerotic nephropathy. Lipids were abundant in the arterial lesions.

Sprague and Orgain,[20] in their study of electrocardiographic changes in coronary occlusion, described the case of a boy of 15 years who had had dyspnea and substernal choking on exertion for three years. At autopsy the coronary arteries showed moderate atheromatous degeneration with calcification. The left circumflex branch was completely occluded by a pinkish gray thrombus, and in the terminal portion of the right coronary artery was a similar clot. Reference was made also to another boy of 15, but the lesion of the coronary arteries was described as "moderate sclerosis" only, and an exact classification cannot be made.

In addition to these examples in the recent literature 2 reports are available in the older literature, but without either microscopic details or illustrations. Dreschfeld [21] in 1890 reported the case "of a boy

18. Jokl, E., and Greenstein, J.: Fatal Coronary Sclerosis in a Boy of Ten Years, Lancet **2**:659 (Nov. 18) 1944.

19. Benda, C.: Ueber einen Fall von schwerer infantiler Koronararteriensklerose als Todesursache, Virchows Arch. f. path. Anat. **254**:600-605, 1925.

20. Sprague, H. B., and Orgain, E. S.: Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital 1914-1934, New England J. Med. **212**:903-910 (May 16) 1935.

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of 12 years who died suddenly in the street whilst running quickly." The coronary arteries were described as being "most markedly affected with atheroma." Two years later, Wild,[22] discussing the pathology of the coronary arteries, described the case of a girl of 12 years (his case 111), who was reported to have died suddenly. No cause was observed other than advanced atheroma of the coronary arteries.

None of the deaths of infants and children in my material was considered to be due to arteriosclerosis.

IV. SYPHILITIC ARTERITIS

In syphilis the coronary arteries are generally involved by narrowing or closure of their ostiums as part of a syphilitic involvement of the ascending aorta. The importance of this process as a complication of syphilis in adults has been discussed frequently.[23] Involvement of that portion of the coronary artery distal to its ostium also may occur, usually in the form of intimal proliferation; this, however, is of far less frequent occurrence, and some authors doubt its existence.[23c] Syphilitic aortitis is usually a feature of acquired syphilis rather than of congenital syphilis, and thus the lesion of the coronary arteries is also more frequent in adults.

Only 1 report has been found in the literature in which a syphilitic infection was believed the cause of a fatal lesion of the coronary arteries in a child. Anderson's patient,[24] a 5 year old girl, was in apparent good health until the morning of her death. She was known to be ill for only thirty minutes. Autopsy revealed hemopericardium from rupture of the left ventricle. There was stenosis of both coronary arteries, and the descending branch of the left coronary artery was obliterated at the site of the rupture and could not be traced beyond it. In the portion of the artery proximal to the site of rupture the intima was discolored and covered by a thin layer of fibrin. A small thrombus was found in the right coronary artery 1 inch (2.5 cm.) from its origin. Microscopic examination revealed a thickening of the inner coat of the coronary arteries and inflammatory infiltrations in the vicinity of the vessels. The myocardium showed patchy fibrosis. Anderson diagnosed the process as syphilitic endarteritis and stated that evidences

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21. Dreschfeld, J.: On Angina Pectoris and Pseudo-Angina, Practitioner **44**: 28-40 (Jan.) 1890.

22. Wild, R. B.: A Contribution to the Pathology of the Coronary Arteries, M. Chron. **16**:223-235 (July) 1892.

23. (*a*) Benson, R. L.: The Present Status of Coronary Arterial Disease, Arch. Path. **2**:876-916 (Dec.) 1926. (*b*) Moritz, A. R.: Syphilitic Coronary Arteritis, ibid. **11**:44-59 (Jan.) 1931. (*c*) Bruenn, H. G.: Syphilitic Disease of the Coronary Arteries, Am. Heart J. **9**:421-436 (April) 1934.

24. Anderson, J.: A Case of Rupture of the Heart in a Child, Lancet **1**:647-649 (March 27) 1915.

of syphilis were found also in other organs. A few spirochetes were found in the myocardium after careful examination.

In none of the cases in this series of autopsies was a juvenile coronary lesion due to syphilis. Such a case was seen recently by the department of pathology of Duke University, Durham, N. C., however, and with the permission of Dr. W. D. Forbus this case is included in the present report.

CASE 7.[25]—A Negro girl, 12 years old, was seen in the pediatric outpatient clinic with a complaint of falling spells for one week. She was said always to have tired easily on exertion, and one month prior to being seen had experienced pain over the heart for a period of fifteen minutes. Three weeks later she again experienced similar pain and was short of breath; there was also blurring of vision. The child fainted at this time but recovered in five minutes after massage of the chest. The day before being seen at the hospital, she again fainted after moderate exertion; respirations were rapid and shallow.

On physical examination a blood pressure of 104 systolic and 60 diastolic was revealed; the pulse rate was 108 beats per minute. No definite cardiac abnormalities were noted. The patient was seen again four days later. Another attack of precordial pain had occurred; the pain did not radiate and gradually disappeared. An inconstant faint systolic murmur was now heard over the pulmonic area. The patient was given sedatives and told to return in one week. The next morning, however, she again had an attack of fainting and was taken to the hospital but was dead on admission. A diagnosis of coronary disease, probably of syphilitic origin, was made. The patient's mother had had several miscarriages, but four siblings of the patient were in good health. The mother had died at the age of 30 and the father at 28, both reputedly of heart disease. The Wasserman reaction of the child was 4 plus. Mild deafness had been noted; the teeth were peg shaped but not typically hutchinsonian.

Autopsy was performed by Dr. Stedman Smith. The heart weighed 240 Gm. The aortic valve was 60 mm. in circumference; its cusps showed scarring at the bases with separation at the commissures. The ascending aorta showed a diffuse mottled yellow thickening of the intima. The orifice of the right coronary artery was partially occluded by this process, while the ostium of the left coronary artery could be found only by opening the artery in a retrograde direction. Only a small needle (18 gage) could be passed through the ostium. The coronary arteries distal to the ostium showed no thickening of the walls and their lumens were patent. The myocardium of the left ventricle showed slight patchy fibrosis. Microscopic examination of the aorta showed typical syphilitic aortitis. The myocardium revealed scattered areas of old and recent infarction.

It was not determined with certainty whether the syphilitic infection in this case was congenital or acquired, although the former was believed more probable because of the familial history and the age of the patient.

V. EMBOLISM

Numerous examples of coronary embolism as a cause of death have been described in which the patients were adults,[26] but this acci-

25. The clinical history is included by permission of Dr. W. C. Davison, Duke University School of Medicine.

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dent is uncommon in children. The embolus has usually consisted of either bacterial vegetations from heart valves or fragments of mural thrombi, either ventricular or aortic in origin. At least 1 instance of a tumor-cell embolus in an adult has been reported.[27] In the majority of cases death from coronary embolism has been sudden.

The significance of coronary emboli as a cause of death in cases of endocarditis is equivocal. The valvular and other associated lesions in themselves may seem to constitute an adequate lethal factor, but

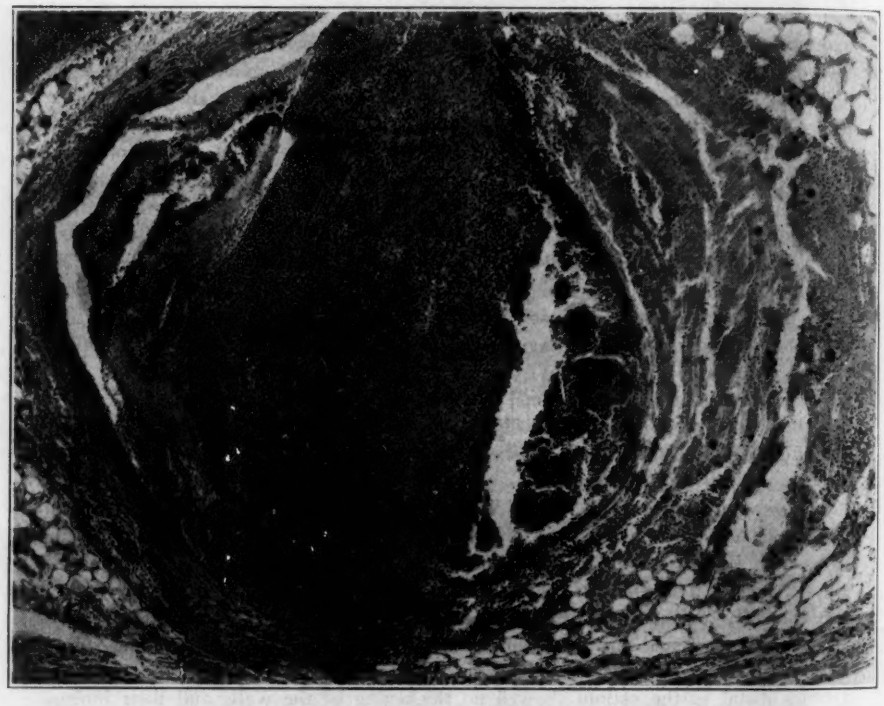

Fig. 4 (case 8).—Embolism of a coronary artery in subacute bacterial endocarditis. Destruction of the wall and acute periarteritis. × 51.

the possibility that coronary occlusion is the immediate cause of death cannot be excluded. Such a case is included in the Michigan series.

Case 8.—An 8 year old girl died with acute thromboulcerative endocarditis of the aortic valve, with septicopyemia (of hemolytic streptococcus origin). Her clinical condition had become progressively worse, and there had been evidence of myocarditis for several days before death. Terminally, severe cyanosis and respiratory difficulty were noted. At autopsy the anterior descending branch of the left coronary artery showed nearly complete occlusion by a large septic embolus

26. Hamman, L.: Coronary Embolism, Am. Heart J. **21**:401-422 (April) 1941.

27. Thompson, T., and Evans, W.: Paradoxical Embolism, Quart. J. Med. **23**: 135-150 (Jan.) 1930.

(fig. 4). There was necrosis of the wall of the artery, and the myocardium contained multpile small abscesses. Other embolic lesions were present in the spleen, kidneys and spinal cord.

A somewhat similar case has been reported by Ramsay and Crumrine,[28] but the evidence was less complete. An infant aged 4 months had symptoms of cardiac distress for one hour before death. At autopsy there was a clot measuring 6 mm. by 13 mm. in the left coronary artery. Microscopic examination showed the clot attached to the arterial wall. There was an inflammatory reaction in all coats of the artery and in the adjacent myocardium. The possibility was sug-

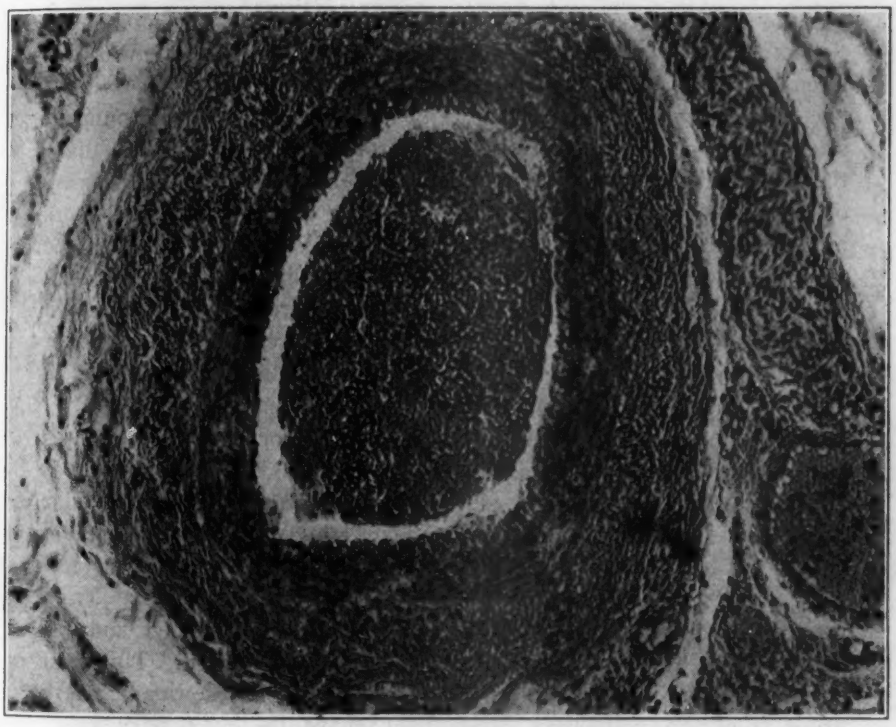

Fig. 5 (case 9).—Embolism in a coronary artery of a newborn infant. × 120.

gested that the clot was a septic embolus. The patient had had an infection of the upper respiratory tract one month previously, and a mural thrombus was present in the left ventricle.

In the local series there is another case which, although not completely proved, may belong in this group.

Case 9.—A boy born prematurely (7½ months) lived for twelve hours. During this time he had much mucus suctioned from his throat, becoming cyanotic

28. Ramsay, R. E., and Crumrine, R. M.: Coronary Thrombosis in an Infant Aged 4 Months, Am. J. Dis. Child. 42:107-110 (July) 1931.

whenever it was permitted to accumulate. His respirations ceased after eleven hours, but he was revived with artificial respiration. After this his color was again good, but his respirations ceased one hour later. In a coronary artery, otherwise normal, microscopic examination revealed an antemortem clot composed chiefly of fibrin but with a few leukocytes included (fig. 5). It is possible that this was an embolus. No source was recognized at the autopsy, but a thrombus had probably formed in the umbilical vein, and a fragment could have reached the coronary artery through the ductus venosus and the still patent foramen ovale. The lungs showed acute edema and the formation of the so-called asphyxial membrane. Whether the clot in the coronary artery was the primary or a contributory cause of death is not certain.

VI. CONGENITAL ABNORMALITIES

Congenital anomalies of the coronary arteries may be of many different types. Among the possibilities are abnormality of origin of one or both arteries, of the structure of the arteries, or of their number, size or distribution. Theoretically, any of these would seem to have the potentiality of producing the effects of conorary occlusive disease on the myocardium and on the clinical course of the patient, and there are numerous reports in the literature in which this is true for the first two types mentioned. Although abnormalities in size or distribution of the arteries are the anomalies most frequently encountered and instances of but a single coronary artery are not rare, sufficient collateral circulation seems always to be present so that no direct ill effect on the heart has been found.[29]

An example of an anomalous origin of one coronary artery[30] was reported by Bland, White and Garland[31] in 1933. The patient was a 3 month old boy who had suffered from recurring dyspnea, pallor and profuse sweating (the pallor and sweating giving the picture of shock) for two weeks. The symptoms were noted especially at certain periods of nursing. An electrocardiogram showed a lesion described as "coronary type." Finally cyanosis developed and the infant died. At autopsy the heart was greatly enlarged. The right coronary artery was essentially normal, but the left coronary artery arose from the pulmonary artery just above the pulmonary valve. The anterior descending branch was of normal size; the circumflex branch was small. The myocardium served by the left coronary artery

29. Krumbhaar, E. B., and Ehrich, W. E.: Varieties of a Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies, Am. J. M. Sc. **196**:407-413 (Sept.) 1938.

30. Because of the similarity of the clinical picture and the effects on the myocardium a discussion of these anomalies is included, even though no "occlusive disease" is present.

31. Bland, E. F.; White, P. D., and Garland, J.: Congenital Anomalies of the Coronary Arteries: Report of an Unusual Case Associated with Cardiac Hypertrophy, Am. Heart J. **8**:787-801 (Aug.) 1933.

showed fibrosis, especially that portion near the endocardium. Associated with the arterial anomaly in this case was a small opening between the inferior vena cava and the left auricle.

Bland and his associates [31] discussed 6 previous reports in which origin of the left coronary artery from the pulmonary artery had been noted, and since their report there have been many similar cases.[32] In all instances of the lesion in infants, the coronary artery arising from the pulmonary artery was the left one. Fibrosis was usually present in the myocardium of the left ventricle and was fairly well confined to that portion served by the anomalous vessel. The maximum age attained by these infants was 12 months. In most of the cases the anomaly of origin was the only malformation present. In some instances the final picture was identical with that seen following coronary occlusion in adults: cardiomegaly, fibrosis of the affected myocardium, ventricular aneurysm and the formation of a parietal thrombosis in the ventricular chamber.[33]

An example of anomalous formation of a coronary artery was reported by Grant.[34] A girl of 14 months had a history of cyanosis and heart failure and was said to have died suddenly. On examination of the heart, blood-filled spaces were seen in the ventricular muscle; these communicated freely with the cavity of the ventricle and with the coronary arteries. The anomaly was interpreted as persistence and growth of the intertrabecular spaces of the myocardium, which normally are reduced to capillaries. A somewhat similar condition was reported by Trevor [35]: An 11 year old girl showed at

32. (*a*) Sanes, S., and Kenny, F. E.: Anomalous Origin of Left Coronary Artery from Pulmonary Artery, Am. J. Dis. Child. **48**:113-122 (July) 1934. (*b*) Bartsch, G., and Smekal, T.: Ueber den Ursprung eines Kranzgefässes aus der Lungenschlagader, Frankfurt. Ztschr. f. Path. **47**:256-261, 1935. (*c*) Chown, B., and Schwalm, F. G.: Congenital Abnormality of the Heart: Left Coronary Artery Arising from Pulmonary Artery, Am. J. Dis. Child. **52**:1427-1429 (Dec.) 1936. (*d*) Linck, K.: Aneurysmatische Erweiterung der linken Herzkammer infolge Ursprungs der linken Kranzschlagader aus der Pulmonalis bei einem 8 Monate alten Mädchen, Virchows Arch. f. path. Anat. **297**:113-118, 1936. (*e*) Barnard, W. G.: Aneurysm of the Left Ventricle Due to the Left Coronary Artery Taking Origin from the Pulmonary Artery, J. Path. & Bact. **47**:345-346 (Sept.) 1938. (*f*) Soloff, L. A.: Anomalous Coronary Arteries Arising from the Pulmonary Artery, Am. Heart J. **24**:118-127 (July) 1942.

33. There are reported cases of similar anomalous arteries in adults in whose hearts no fibrosis occurred.[32f] In these cases either the left or the right coronary artery might be the anomalous vessel.

34. Grant, R. T.: An Unusual Anomaly of the Coronary Vessels in the Malformed Heart of a Child, Heart **13**:273-283 (Dec. 23) 1926.

35. Trevor, R. S.: Aneurysm of the Descending Branch of the Right Coronary Artery, Situated in the Wall of the Right Ventricle, and Opening into the Cavity of the Ventricle, Associated with Great Dilatation of the Right Coronary Artery

(Footnote continued on next page)

autopsy an intramyocardial dilatation of the right coronary artery, believed to be a congenital aneurysm. This had ruptured into the ventricular cavity and may have been a contributing factor in the child's death. Malet [36] found rupture of a coronary aneurysm as the cause of the sudden death of a 5 year old boy. Details are not furnished, and the congenital nature of the lesion can only be inferred.

In this series of autopsies, there is no example of anomalous formation of the coronary arteries in which death can be attributed to the coronary lesion alone. All the lesions of ectopic origin are associated with other malformations. A boy living two days showed at autopsy a single coronary artery arising from the transverse aorta, but there was also a cor triloculare biatriatum, an absence of the ascending aorta and other anomalies; these dysplasias were in themselves sufficient to cause death.

VII. RHEUMATIC ARTERITIS

Reference was made in the introduction to the recent study by Weinstein[2] in which clinical symptoms and electrocardiographic observations identical with those of coronary occlusion on the usual arteriosclerotic basis were found on examination of young adults suffering from rheumatic fever. The cases reported were all patients over 20 years of age, but examples of similar conditions can be found frequently in persons less than 17 years old. Inflammatory involvement of the coronary arteries in rheumatic fever is known to occur often,[37] with involvement of the smaller branches more frequent than that of the main stems. The lesions are degenerative, necrotic and proliferative and have been carefully described by Gross, Kugel and Epstein.[37c] In their discussion of 100 cases of active and inactive rheumatic fever in patients of all ages, there were included 3 instances of "thrombosis of myocardial arteries directly attributable to rheumatic injury of the vessel rather than to a primary or secondary sclerotic vascular damage" in children. Some of the affected vessels showed an acute necrotizing arteritis. Thrombosis of the left circumflex artery, including the main trunk, was found in an infant of 17 months, and extensive myocardial infarction was present.

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and Non-Valvular Infective Endocarditis, Proc. Roy. Soc. Med. (Sect. Stud. Dis. Child.) **5**:20-26, 1911-1912.

36. Malet: Aneurysm of Coronary Artery; Rupture; Necropsy; Remarks, Lancet **2**:67 (July 9) 1887.

37. (*a*) Karsner, H. T., and Bayless, F.: Coronary Arteries in Rheumatic Fever, Am. Heart J. **9**:557-585 (June) 1934. (*b*) Fraser, A. D.: Coronary Endarteritis in Acute Rheumatism, Arch. Dis. Childhood **9**:267-276 (Oct.) 1934. (*c*) Gross, L.; Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, Am. J. Path. **11**:253-279 (March) 1935.

In some instances these thrombi may become organized and the vessel canalized. A more unusual example was reported by Rae.[38] A boy of 2 years and 9 months died suddenly on his tenth day of hospitalization. At autopsy acute rheumatic myocarditis and pericarditis were found. There were large aneurysmal dilatations in both coronary arteries, and thrombosis had occurred in the aneurysm of the right coronary artery. Although the artery was occluded infarction had not yet developed.

No attempt has been made to find all the reported examples of coronary occlusion occurring as a result of rheumatic fever in children. The

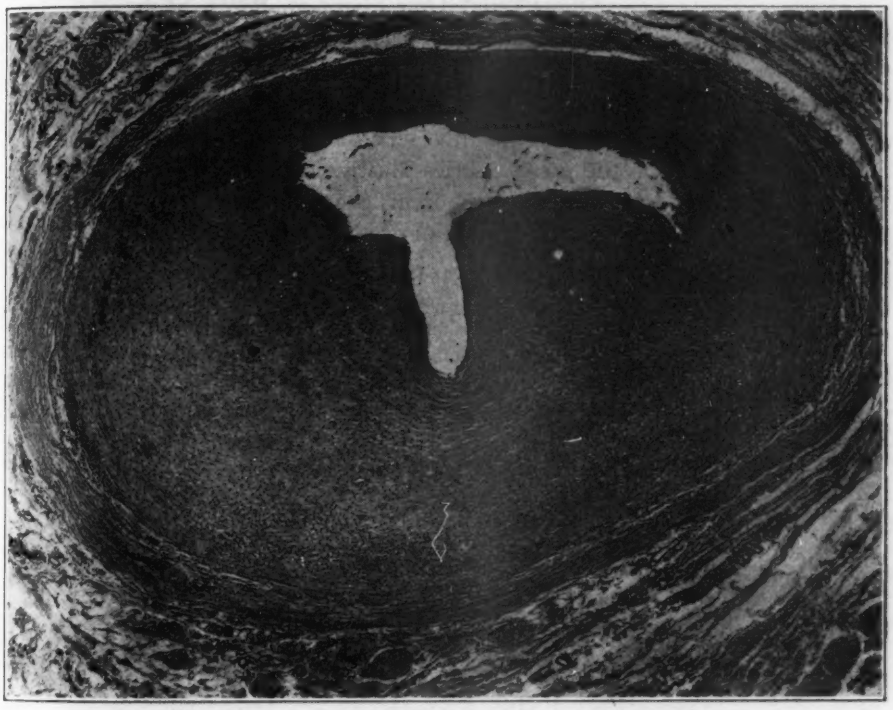

Fig. 6 (case 10).—Pronounced fibroblastic proliferation of the intima of a coronary artery associated with hypertension of renal origin. × 40.

previously mentioned citations show the existence and nature of the process.

In this series of autopsies no examples of coronary occlusion due to rheumatic fever were found. This was possibly the result of routine examination of the coronary arteries only in cases in which a sufficient cause of death was not otherwise obvious.

38. Rae, M. V.: Coronary Aneurysms with Thrombosis in Rheumatic Carditis, Arch. Path. **24**:369-376 (Sept.) 1937.

VIII. HYPERTENSION

A proliferation of the intima of many of the large and medium-sized arteries of the body is frequently seen in persons in whom hypertension has been present, regardless of its cause. This lesion has been related to the increased intravascular pressure. Although more frequent in adults, this lesion is also seen in children. In most instances the basic lesion will prove lethal to the patient; thus renal dysfunction may cause death from uremia. In a few instances the secondary vascular changes may be of chief significance. No instance has been found in which this was true of the involvement of the coronary arteries, but Kremer [39] has reported the case of a 14 year old girl with bilateral paragangliomas of the adrenal glands in whom the blood pressure had been 206 systolic and 152 diastolic. At autopsy there were revealed myocardial hypertrophy and pronounced sclerosis of the coronary arteries. Death was due to cerebral thrombosis.

Hypertension is most frequently seen as a result of renal lesions. One of the cases in the present series illustrates the changes in the coronary arteries of children that may occur as a secondary feature. However, hypertension was not the cause of death in this instance.

CASE 10.—A girl 11 years of age was hospitalized for chronic nephritis. The blood pressure one month before death was 214 systolic and 164 diastolic. Her symptoms and the results of chemical studies of the blood were those of uremia, and at autopsy the kidneys showed an active chronic glomerulotubular nephritis with secondary contraction. A main stem coronary artery showed a pronounced fibroblastic proliferation of the intima, with apparent reduction in the size of the lumen (fig. 6). A small area of hemorrhage was seen in the myocardium, but there was no necrosis or infarction.

SUMMARY

Coronary occlusive disease can occur in infants or in children and may be a cause of death in such patients. From a series of autopsies and from the literature cases have been assembled illustrating the eight types of lesions which may be found. These eight types include: medial calcification with fibroblastic proliferation of the intima, polyarteritis (periarteritis) nodosa, arteriosclerosis (atherosclerosis), syphilitic arteritis, embolism, congenital abnormalities, rheumatic arteritis and intimal proliferation, due to hypertension.

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39. Kremer, D. N.: Medullary Tumor of the Adrenal Glands with Hypertension and Juvenile Arteriosclerosis, Arch. Int. Med. **57**:999-1007 (May) 1936.

Obituaries

FRANK SPOONER CHURCHILL, M.D.
1864-1946

Frank Spooner Churchill was born on Aug. 28, 1864 at Milton, Mass. He received his A.B. degree from Harvard University in 1886 and his M.D. from the same university in 1890. He served as intern at the Massachusetts General Hospital in 1891. After his term of service at the hospital he accepted a position as surgeon to the Calumet and Hecla Mining Company of Northern Michigan during the years 1891 and 1892.

He located in Chicago in 1892, where he specialized in pediatrics and in which he continued to specialize with great zeal for thirty years. He was greatly interested in hospital work, medical education and community interests. In his early days of practice, when diphtheria raged widely throughout the city, he had extensive experience with the administration of the newly discovered antitoxin as well as with introduction of intubation tubes in laryngeal stenosis. These opportunities came to him while he occupied the official position of medical inspector of the Chicago Board of Health. In 1905 in association with others, he successfully passed the civil service examination which entitled him to become attending pediatrician at the Cook County Hospital. He was also associate professor of pediatrics at Rush Medical College; attending physician at the Children's Memorial Hospital for ten years; attending physician at the Presbyterian Hospital also, and Director of the Milk Commission. He served as physician for the Juvenile court of Chicago and was a member of the Juvenile Psychopathic Institute and the Infant Welfare Society of that city. He was the first chief editor of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, and served in that capacity from 1911 to 1919.

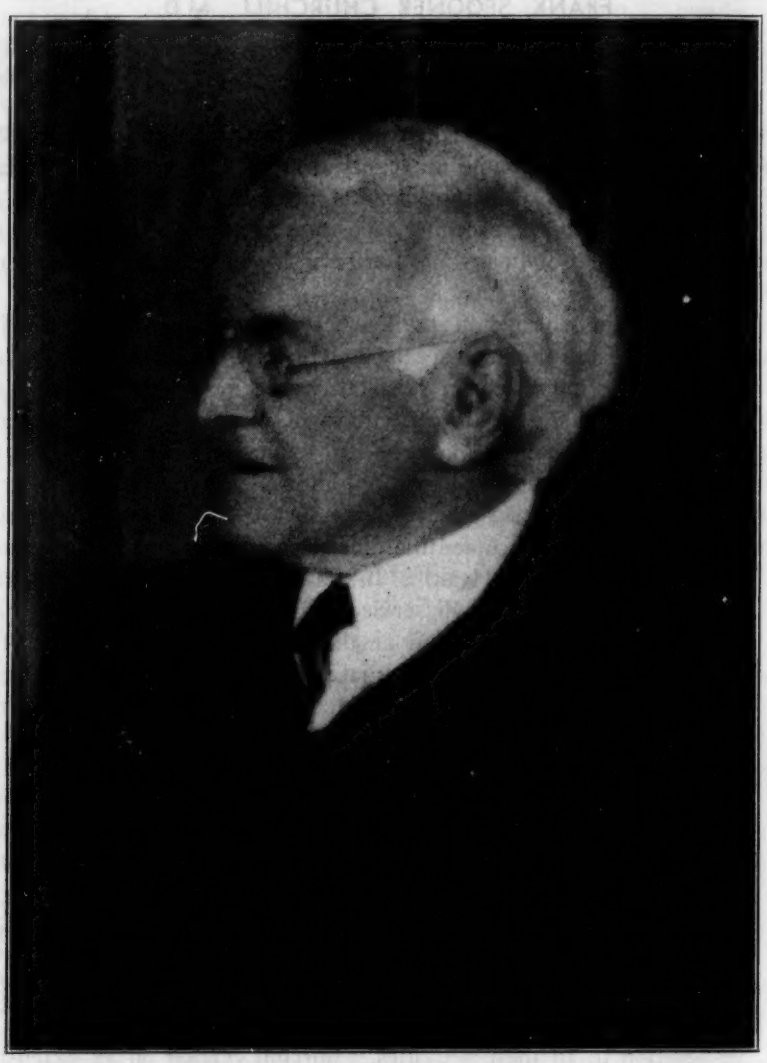
During World War I he served as major in the Medical Corps, of the United States Army Reserve Corps, first in the Base Hospital at Newport News, Va., and later at Camp Devens, Mass., in 1917. He was honorably discharged in 1919.

In addition to all these activities, Churchill carried on an extensive private practice. He showed boundless energy and a keen and penetrating interest in the welfare of his patients. In his personal relations with others he was dignified and affable though formal.

He wrote on a variety of subjects, among which may be mentioned "Acute Leukemia" and "The Wet Nurse in Hospital Practice." In

1909 he made an extensive report on "The Medical Work of the Juvenile Court of Cook County." He also wrote on "The Urine of Normal Children" and later on "Serological Tests for Syphilis."

He remained a devoted disciple of his master and teacher at Harvard, Thomas Morgan Rotch. Churchill was an ardent western exponent



FRANK SPOONER CHURCHILL, M.D.
1864-1946

of Rotch's modified milk on "the percentage basis." He had great faith and persisted in the use of this plan of feeding infants as originated by his revered teacher.

He was elected to membership in the American Pediatric Society in 1897; was president of this organization in 1917, and Chairman of the Section of Pediatrics of the American Medical Association, 1913-1914.

After his military service in 1919 he returned to his native Milton, Mass., where he practiced for a time and was appointed medical director of schools in 1919; he was also appointed medical assistant to Judge Baker, Guidance Clinic, Boston.

After retiring from his practice at Milton, he moved to Bass River, Yarmouth, Cape Cod, where he spent his last years. He married Lucretia Mott Hallowell Dec. 21, 1894; they have two surviving children. Churchill died in the Faulkner Hospital, Boston, Feb. 27, 1946, aged 81 years, of heart disease.

CHESTER ARTHUR STEWART, Ph.D., M.D.
1890-1946

A career characterized by scientific achievement, successful private practice and devotion to teaching together with participation in both professional and lay activities directed toward improvement of the health of children was brought to a premature close by the sudden death on Feb. 8, 1946, of Dr. Chester A. Stewart, Professor and Director of the Department of Pediatrics, Louisiana State University School of Medicine.

A native of Hannibal, Mo., born Nov. 6, 1890, Dr. Stewart received the B. A. degree from the University of Missouri in 1914, after which he had the good fortune to become associated with Dr. C. M. Jackson, with whom early studies were made on inanition and growth. Later, he conducted studies on vital capacity. The intensity of his efforts is revealed by the degrees awarded him by the University of Minnesota: M.A. 1915; Ph.D. (Anatomy) 1917; M.D. 1919, and Ph.D. (Pediatrics) 1921. He developed an intense interest in the problem of tuberculosis in children and assisted in the development of the Lymanhurst Health Center in Minneapolis. Although engaged in an active private practice, he continued to carry on teaching responsibilities, and in 1936 he was made clinical professor of pediatrics at the University of Minnesota.

It was his genuine interest in teaching and research which caused him to accept a full time teaching position at Louisiana State University School of Medicine, in New Orleans. Developments of a political nature compelled him to devote active efforts to maintaining the highest ideals of medicine. His new friends in the South as well as his former colleagues feel keenly this loss to society and to pediatrics.

Dr. Stewart was a member of the American Academy of Pediatrics, the American Medical Association, the state medical associations of Louisiana and Minnesota, the Louisiana State Pediatric Society, the National Tuberculosis Association and the Tuberculosis Association of Louisiana, and at one time was president of the Hennepin County Medical Society and the Northwestern Pediatric Society. In 1937 he was a delegate to the Fourth International Congress of Pediatricians, in Rome. His scientific publications numbered some eighty articles in addition to contributions in textbooks, and as editor he initiated the annual publication of the pediatric numbers of the *Journal Lancet* and the *New Orleans Medical and Surgical Journal*. He was a member of Sigma Xi. Dr. Stewart is survived by his wife and three sons.

A. E. H.

Abstracts from Current Literature

Biochemistry, Bacteriology, and Pathology

THE CONCENTRATIONS OF CERTAIN ANTIBODIES IN GLOBULIN FRACTIONS DERIVED FROM HUMAN BLOOD PLASMA. J. F. ENDERS, J. Clin. Investigation **23**:510 (July) 1944.

The fractionation of normal human plasma collected by the American Red Cross yields a gross fraction comprised of alpha, beta and gamma globulins which contains a large proportion of the antibodies reacting with a variety of pathogenic bacteria and their products, viruses and the isoantigens of the human blood groups, in a concentration four to ten times that of plasma. The normal gamma globulins have been further separated and concentrated to yield a preparation containing antibodies (against diphtheria toxin, streptococcic erythrogenic toxin, influenza A virus, mumps virus and the H antigen of Eberthella typhosa) in a concentration of from fifteen to thirty times that of the titer of pooled plasma. In solutions concentrated to at least twenty-five times the titer of plasma pool, the titer of certain of the antibodies was comparable with or greater than titers of corresponding convalescent serums.

Immunologic assay of the antibodies in 62 preparations of gamma globulins derived from plasma collected in various sections of the United States revealed a general uniformity of potency.

The implications of these observations to the standardization of the gamma globulins as an agent in the prophylaxis and therapy of disease are discussed, together with their significance in respect to the nature of normal human antibodies.

GUEST, Cincinnati.

VIOLACEIN, AN ANTIBIOTIC PIGMENT PRODUCED BY "CHROMOBACTERIUM VIOLACEUM." HERMAN C. LICHSTEIN and VIRGINIA F. VAN DE SAND, J. Infect. Dis. **76**:47 (Jan.-Feb.) 1945.

Violacein, the purple pigment produced by Chromobacterium violaceum, was extracted, purified and tested for antibiotic activity against representative microorganisms. It had a pronounced inhibitory effect on the growth of gram-positive bacteria with the exception of Clostridium welchii but had little effect on proliferation of gram-negative bacteria except for the susceptible meningococcus. Of the molds tested only Blastomyces dermatitidis was strongly susceptible to the action of the pigment. The activity of violacein is influenced only slightly by the number of bacteria in the test inoculum but is influenced greatly by the presence of serum.

TOOMEY, Cleveland.

Vitamins; Avitaminoses

HEPATIC DAMAGE IN INFANTILE PELLAGRA AND ITS RESPONSE TO VITAMIN, LIVER AND DRIED STOMACH THERAPY AS DETERMINED BY REPEATED LIVER BIOPSIES. THEODORE GILLMAN and JOSEPH GILLMAN, J. A. M. A. **129**:12 (Sept. 1) 1945.

This study is based on biopsies of the livers of 20 children suffering from severe malnutrition and pellagra at the time of admission to the Non-European Hospital in Johannesburg, South Africa. The characteristic pathologic appearance was a varying degree of fatty change involving almost every cell, with a loss of hepatic architecture. A biopsy of the liver proved a better prognostic guide than did the clinical picture.

In addition to an adequate diet, 7 children were given vitamin therapy. All died. Biopsy showed progressive changes in the liver. Seven children were given liver extract, and 5 recovered. Biopsies revealed a slow disappearance of fat from the liver despite the clinical recovery. Six children were given dried stomach in doses of 10 Gm. daily in combination with hydrochloric acid. Clinical response was rapid in all cases, and biopsies showed a rapid disappearance of hepatic fat.

It is suggested that the accumulation of fat in the liver and its excretion in the feces in this condition are due to conversion of carbohydrates into fat which is not utilized. Dried stomach must be regarded as a vigorous lipotropic substance.

Recurrent attacks of overt or subclinical malnutrition with resulting damage to the liver may explain the high incidence of cirrhosis and of primary carcinoma of the liver among young South African Negroes.

BAIRD, Wauwatosa, Wis.

INVESTIGATIONS OF VITAMIN A CONTENT OF HUMAN BODY FLUIDS. W. TOMASZEWSKI and L. DZIALOSZYNSKI, Edinburgh M. J. **52**:74 (Feb.) 1945.

Although there is a fair amount of information about the vitamin A content of the blood in various states of health and of disease and about the content of human milk, the knowledge is scanty as to the amount in other body fluids. The authors investigated from this standpoint the fluid of pleurisy, ascites and pericarditis. The cerebrospinal fluid appears to be vitamin free, while amniotic fluid contained vitamin A in 2 cases of the 6 in which an examination was made. Vitamin A is common in pathologic fluids, such as that of pleurisy, in which carotene was also found. There seems to be no relationship between the protein content and the presence of vitamin A or between the presence of vitamin A in the urine and its presence in the fluids. How these substances reach the body cavities is not always known; therefore the significance of vitamin A in such fluids is not known.

NEFF, Kansas City, Mo.

Hygiene; Growth and Nutrition; Public Health

THE ORGANIZATION OF THE SPEECH IMPROVEMENT AND CORRECTION PROGRAM IN OREGON. LEON LASSERS, Quart. J. Speech **31**:207, 1945.

In view of the problems met in developing the statewide program for speech improvement and correction in Oregon, more than three-fourths of the schools there are classified as rural or semirural. Approximately 70 to 75 per cent of the speech difficulties of the school children in Oregon are of an articulatory nature. Teachers should be given material in their training courses in the recognition and correction of such disorders. The author feels that there has been too much emphasis on providing specialists and that the classroom teacher should be trained. Even the speech specialist cannot perform his work adequately in the public school system without the wholehearted cooperation of the classroom teacher. For this cooperation, it is necessary that the classroom teacher have some elementary training.

PALMER, Wichita, Kansas.

Prematurity and Congenital Deformities

DISCUSSION ON NUTRITION OF THE PREMATURE INFANT IN THE FIRST MONTH OF LIFE. HELEN M. M. MACKAY, Proc. Roy. Soc. Med. **38**:57 (Dec.) 1944.

Mackay discusses in detail the feeding of the premature infant. She points out that a baby that is kept warm will swallow and suck better than a cold baby. She gives the caloric requirements of babies according to their weights and names the various types of milk that are best tolerated. As soon as the baby is well established on his feedings, vitamin D is added, and then ascorbic acid is given.

Her paper is accompanied with four tables. Table 1 shows the composition and caloric value of colostrum and early breast milk. Table 2 shows the caloric

intake in the first eight days of life of 20 consecutive breast-fed babies. Table 3 shows mixtures and solutions containing approximately 20 calories per fluidounce (0.75 calory per cubic centimeter). Table 4 shows the caloric intake of premature babies in the first two weeks of life.

Dr. V. Mary Crosse and Dr. J. N. O'Reilly also took part in the discussion.

WILLIAMSON, New Orleans.

PECULIAR ASSOCIATION OF GENITAL MALFORMATION WITH DEFECT OF THE OLFACTORY BRAIN. B. GRUENFELDER and W. LASCH, Acta oto-laryng. orient. **1**:6, 1945.

The authors discuss the relation between olfactory and genital functions. They feel that in a certain number of cases there is a correlation of olfactory defects and eunuchoidism. They cite the case of a man 34 years old who committed suicide. He was born with very small genital organs, bilateral cryptorchidism and bilateral inguinal hernia. Puberty failed to appear. From the age of 5 years he had suffered from hay fever and asthma, and his sense of smell was underdeveloped. The autopsy record showed hypoplasia of the penis, the scrotum and the testicles. There was agenesis of the right portion of the prostate with hypoplasia of the left as well as aplasia of the right kidney and absence of the right ureter. There was agenesis of the left olfactory nerve with hypoplasia of the right. The patient had a female build, with no hair on the trunk. The distribution of the hair over the genital organs was distinctly of the female type. The authors' impression is that this was a case of eunuchoidism associated with cryptorchidism and aplasia or remarkable hypoplasia of the olfactory nerves.

The authors have collected 12 cases, in 11 of which hypoplasia or aplasia of the olfactory nerves was associated with malformation of the genital organs, and they conclude that in practically every case of congenital defect of the olfactory part of the brain, hypoplasia of the sex glands can be expected. Normal development of the olfactory part of the brain does not, however, preclude the presence of genital malformation, including hypoplasia of the sex glands.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Newborn

PNEUMOCOCCUS MENINGITIS IN THE NEWBORN: REPORT OF A CASE WITH RECOVERY AND A REVIEW OF THE LITERATURE. PAUL HOGG and CHESTER D. BRADLEY, J. Pediat. **26**:406 (April) 1945.

The case of a 13 day old baby who had pneumococcic meningitis and survived is reported. A review of all available literature indicates that this is the third case in which recovery occurred. Twenty-eight cases of pneumococcic meningitis in the newborn have been reported. Meningitis in the newborn is not always suspected because the symptoms are not typical. In 11 (40 per cent) of the 28 cases reviewed a diagnosis was made during life, by lumbar puncture; in 17 cases (60 per cent) diagnoses was made at autopsy. In 23 cases (82 per cent) the disease was of primary origin. In only 4 cases was it of secondary origin. In 3 of these 4 cases pneumonia was observed at autopsy, and in the other case otitis media was found. In the authors' case the patient was treated with sulfadiazine. Of the other 2 patients who recovered, 1 was treated by means of repeated spinal puncture, and the other made a spontaneous recovery.

AUTHORS' ABSTRACT.

HAEMOLYTIC DISEASE IN ONE DIZYGOTIC TWIN. F. STRATTON, F. A. LANGLEY and U. LISTER, Brit. M. J. **1**:151 (Feb. 3) 1945.

This article reports the cases of twins born to a 28 year old mother, this being her second pregnancy. The girl weighed 3 pounds 10 ounces (1,590 Gm.) at

birth, and the boy weighed 4 pounds (1,814 Gm.). There were two placentas with separate amniotic sacs. Within six hours of birth the boy showed jaundice and twenty-eight hours after delivery there was a decided drop in his red cell count. On the third day his red cell count had dropped to 1,850,000. This child died on the fourth day of life. The girl gained weight steadily and never showed any jaundice and on the fifth day her hemoglobin content was 100 per cent, and the number of red blood cells 5,000,000. At six weeks of age she weighed 5 pounds 8 ounces (2,495 Gm.). The pathologic changes in the boy were consistent with erythroblastosis. The mother was shown to have Rh-negative blood (rhrh). The affected child was of genotype Rh_1 rh. The unaffected one was Rh″ rh. It seems that the father is therefore Rh_1 Rh″.

The maternal Rh antibodies were of the type anti-Rh′ and showed an increase in titer during the first few weeks after birth of the child. It was shown that while they reacted strongly with cells of a genotype similar to that of the affected child, they completely failed to react with erythrocytes of a genotype like those of the unaffected infant.

BIRDSONG, University, Va.

NURSING OF THE NEWBORN DURING THE FIRST THREE DAYS. G. ARAOZ FRAZER. Rev. colomb. de pediat. y puericult. **2**:58 (Dec.) 1942.

This author considers a nonphysiologic loss of weight that which occurs during the first days and is due to poor feeding. He recommends the use of dextrose and maltose every three hours in a 5 per cent solution, given in quantities proportionate to the children's needs. In this form the loss of weight is reduced to less than 100 Gm.

LOZOYA, México, D. F., Mexico.

THE PROBLEM OF INFANTILE MORTALITY IN COLOMBIA. BELIZARIO LOPERA, Rev. colomb. de pediat. y puericult. **2**:61 (Dec.) 1942.

In 1940, the death rate in Colombia of infants up to 12 months of age was 151.2 per thousand born alive. The principal causes were diarrhea, enteritis, diseases of the gastrointestinal tract due to disorders in feeding and infections of the respiratory tract.

The main problem lies in the economic difficulties. In 1937 only 3.2 per cent of the Health Service budget was spent by the Board of Infant Welfare. In 1941 it was raised to 7.4 per cent.

LOZOYA, México, D. F., Mexico.

SOME CONSIDERATIONS REGARDING THE CEPHALHEMATOMA. CARLOS WERNECK, Rev. de ginec. y d'obst. **1**:7 (Feb.) 1942.

The author shares the opinion of Maygrier and Jeanin that cephalhematoma can be produced in the fetus with a small and badly ossified head and not necessarily when the head is large and the maternal pelvis is narrow. The hematoma results from the straightening of the bone, with vascular ruptures of the poorly ossified external layer. This can be called a pathologic cephalhematoma.

The traumatic hematoma can also occur as a consequence of the trauma suffered by the fetus during delivery.

LOZOYA, México, D. F., Mexico.

DACTYLOSCOPIC IDENTIFICATION OF THE NEWBORN. AGUIRRE HOTA BARBOSA, Rev. de ginec. y d'obst. **1**:14 (Jan.) 1943.

The author proposes to make a dactyloscopic identification of every child born alive. He states that this method is better than any other for identification.

LOZOYA, México, D. F., Mexico.

Acute Contagious Diseases

SEROLOGIC TYPES OF HEMOLYTIC STREPTOCOCCI ISOLATED FROM SCARLET FEVER IN MASSACHUSETTS, 1942-1943. S. M. WHEELER and G. E. FOLEY, New England J. Med. **231**:287 (Aug. 24) 1944.

Hemolytic streptococci associated with scarlet fever in certain Massachusetts cities during 1942 and 1943 were predominantly of types 2, 1, 8 and 19 in that order of frequency. During this period there was some shifting in relative order of frequency among the predominant types, although type 2 maintained itself as a major cause of scarlet fever.

AUTHORS' SUMMARY.

CHICKENPOX, HERPES ZOSTER, AND ACUTE ANTERIOR POLIOMYELITIS. JOHN C. MCGARRAHAN, New York State J. Med. **45**:193 (Jan. 15) 1945.

The author discusses the possible relationship between chickenpox (varicella) and herpes zoster. He also reports on the beneficial effects of intravenously administered thiamine hydrochloride on 3 patients with chickenpox, the pain and intense pruritus being relieved in six hours.

A case history of a family is presented in which poliomyelitis, herpes zoster and chickenpox occurred within a three to four week period, and the question is raised as to the possible relationship of these diseases.

Finally a case history is presented of an 8 year old girl with acute anterior poliomyelitis who was apparently benefited by the intravenous administration of thiamine and nicotinic acid.

DAVIS, Rochester, N. Y.

ELECTROCARDIOGRAPHIC CHANGES IN EPIDEMIC PAROTITIS (MUMPS). D. H. ROSENBERG, Proc. Soc. Exper. Biol. & Med. **58**:9 (Jan.) 1945.

The observation of heart block in 2 white sailors, each aged 20, with epidemic parotitis prompted study of the electrocardiogram in patients with this disease. Tracings were obtained from 104 adults with mumps during the height of an epidemic in 1944, and for 46 of the patients serial tracings were made. Significant changes in the tracings were found for 16 patients (15.4 per cent). In all these subjects changes in the T wave were found, and in 14 more than one abnormality was present. Other changes observed were abnormalities in the P wave, the P-R interval, the QRS complex and the S-T segment. No specific electrocardiographic pattern was recognizable. The majority of the changes were observed from the fifth to the tenth day of the disease, and the pattern returned to normal in two to thirty-five days (in most patients in four to eight days). In 2 cases residual changes persisted for three and five months, respectively. Precordial pain was found in 4 patients, systolic murmur in 2, increase in sedimentation rate in 5 and leukocytosis in 4.

HANSEN, Galveston, Texas.

INFLUENCE OF THIAMINE DEFICIENCY IN MACACA MULATTA ON SUSCEPTIBILITY TO EXPERIMENTAL POLIOMYELITIS. P. F. CLARK, H. A. WAISMAN, H. C. LICHSTEIN and E. S. JONES, Proc. Soc. Exper. Biol. & Med. **58**:42 (Jan.) 1945.

The intranasal instillations of the MV strain of poliomyelitis virus in 40 Macacus mulatta monkeys which were maintained on thiamine-deficient diets were made to determine the effect of a deficiency of this vitamin on the susceptibility of this species to this virus. The results of this extensive study indicate that there is no increased resistance to the disease in the animal deficient in thiamine.

HANSEN, Galveston, Texas.

GOETTCHE'S TRIANGLE IN PERTUSSIS AND ITS RELATIONSHIP TO PERIFOCAL TUBERCULOUS REACTIONS. E. PINARD, M. LE CHEVALIER DE LA SAUZAYE and P. DURRIBERE, Arch. am. de med. **19**:25, 1943.

In this paper the authors bring forth the necessity of clearing up the true nature of various pulmonary lesions which have been frequently described in the course of whooping cough. At present there is still disagreement as to whether they are due to the disease itself or to an exacerbation of a preexistent tuberculous process.

Among the lesions referred to, the most important from the standpoint of the roentgenologist are the following: enlargements of peribronchial and tracheobronchial lymph nodes, changes in position of the diaphragm, increases in hilar shadows and bronchovascular markings and the "basal triangle" of Goettche. The latter is defined as a triangular radiologic density located at the right cardiophrenic angle, which begins at the hilus and extends downward and outward. Therefore the apex is located at the hilus and the base away from it.

The authors cite the experience of Invaldi and Puig, who found Goettche's triangle in 52 per cent of 129 cases of pertussis.

The case of a 3½ year old child who showed a typical "basal triangle" in the course of pertussis is described. The tuberculin reaction was negative, and the sedimentation rate was not accelerated.

ABALLI, Habana, Cuba.

ASPECTS OF THE DIPHTHERIA PROBLEM IN FLORIDA, URUGUAY. FERNANDO ABENTE HAEDO and MARIO J. BONILLA, Bol. Inst. internac. am. de protec. a la infancia **18**:470 (Sept.) 1944.

The authors made an epidemiologic study of diphtheria in Florida, Uruguay, examining various aspects of the disease and pointing out the frequency of diphtheria in adults.

They show the deficiencies of the present system of reporting the infectious diseases, which makes it impossible to obtain an exact information on these conditions, and they propose a new, simple and practical method that corrects those disadvantages.

AUTHORS' SUMMARY.

EXAMINATION COMPLICATIONS AND SEQUELAE IN SCARLET FEVER OF INFANTS. M. SCHACHTER, Ann. pædiat. **163**:151 (Aug.-Sept.) 1944.

Complications involving the central nervous system in scarlet fever are rare. The existence of these, however, may not be disputed. The commonest forms are hemiplegic with or without complications; on the other hand, extrapyramidal lesions are very rare. Description of three personal observations of patients with choreoathetosis are given, and 5 cases are cited from the literature. The pathogenesis is not clear. Individual disposition plays a role.

AUTHOR'S ABSTRACT.

OBSERVATIONS DURING AN EPIDEMIC OF POLIOMYELITIS. K. G. DHUNÉR, Nord. med. (Hygiea) **24**:2187 (Dec. 8) 1944.

The author reports on 307 cases of infantile paralysis observed in a district of Sweden in 1943. Of these cases 79 were of the nonparalytic type. Twenty-seven of the patients died. During the epidemic 22 pregnant women acquired poliomyelitis. Four of them died before parturition; 5 had miscarriages; 2 had stillborn infants; the fate of 1 is unknown, and 10 gave birth to healthy children. In none of the latter did paralysis or muscular atrophy occur. A boy of 15 had been treated at a hospital, one year previously, for a meningitic type of poliomyelitis and displayed also this time a nonparalytic poliomyelitis.

WALLGREN, Stockholm, Sweden.

ACUTE INFECTIOUS DISEASES IN INFANCY. GUNNEL MELIN and KARL-AXEL MELIN, Nord. med. (Hygiea) **24**:2213 (Dec. 15) 1944.

The authors report 26 cases of scarlet fever, 43 cases of measles, 22 cases of German measles and 23 cases of chickenpox in infants treated at the Hospital for Epidemic Diseases of Stockholm during the years 1934 to 1943. All infants with scarlet fever recovered, although severe complications occurred in many instances. Two newborn infants were treated for measles at the same time as their mothers, who contracted the disease during labor. Complications were frequent in infants with measles, and 2 children died. The rubella and chickenpox were very benign.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

CORRELATION OF SYMPTOMATOLOGY WITH ENTEROZOIC PARASITISM IN CHILDREN. ROYAL L. BROWN, J. Pediat. **26**:291 (March) 1945.

An independent correlation of symptomatology with parasitism was made on 345 parasitized 6 week to 12 year old patients of the pediatrics department of the Philadelphia General Hospital.

The survey showed that 7 of the 41 patients with Endamoeba histolytica had acute, moderately severe, nonfulminating dysentery with five to fifteen copious, loose daily stools accompanied with tenesmus. Tenderness of the right iliac fossa was present in all 7. Eleven others had recurrent diarrhea with intermittent constipation. Twenty-three were asymptomatic carriers. Thirty-four (83.9 per cent) of these patients with amebiasis had on admission no symptoms ascribable to parasitism. Emetine hydrochloride and carbarsone gave good therapeutic results.

Endamoeba coli, Endolimax nana, Iodamoeba bütschlii and Dientamoeba fragilis in cases without significant hyperparasitism produced no ascertained clinical symptoms.

Fifteen of the 165 patients with giardiasis had acute generalized abdominal aches and pains, intermittent diarrhea and constipation. All 15 were inattentive, irritable and moderately flatulent. Twenty-three had had repeated diarrhea suggestive of giardiasis. The remainder (77 per cent) were and had been free from symptoms of giardiasis. Quinacrine hydrochloride relieved the acute symptoms and decreased the density of parasites. One child with innumerable Chilomastix mesnili organisms and another with many Trichomonas hominis organisms had diarrhea without other determined cause. No treatment was instituted.

Two of the 3 patients with ascariasis had abdominal aches and tenderness and colicky epigastric episodes. They were underweight. The third patient had no symptoms of ascariasis. Hexylresorcinol relieved the symptoms; several worms were discharged during treatment.

Twenty of the 21 patients with enterobiasis had pruritis ani, with disturbed sleep and inattentiveness. Gentian violet medicinal was therapeutically effective.

One patient infected with Trichuris trichiura had acute symptoms of periodic diarrhea, tender colon, anemia and malnutrition; the other had no such symptoms. Hexylresorcinol relieved these symptoms during hospitalization.

Only 4 of the 6 patients infected with Taenia sp. had flatulence, constipation and diarrhea, malnutrition, erratic appetite and abdominal tenderness. Aspidium gave good therapeutic results.

Stools from children with gastroenteritis of causation other than parasitism had comparatively few parasites. Infections of the upper respiratory tract were more frequent in parasitized (50.5 per cent) than in nonparasitized (32.3 per cent) children; similarly, recurring infections of the upper respiratory tract were correspondingly higher.

AUTHOR'S ABSTRACT.

COMMUNITY ORGANIZATION FOR THE CONTROL OF RHEUMATIC FEVER. DONALD B. ARMSTRONG and GEORGE M. WHEATLEY, New York State J. Med. **45**:169 (Jan. 15) 1945.

The purpose of this paper is to suggest a plan for community action in the control of rheumatic fever and to urge physicians interested in the disease to help initiate such a community organization.

The authors discuss the magnitude of the problem presented by rheumatic fever and stress the need for organized action. They point out the similarity of many features of rheumatic fever to tuberculosis and suggest that a study of the method and results of the Framingham Tuberculosis Demonstration might be of value. They emphasize the necessity of reporting and registering cases of rheumatic fever, of community education, of a good consultation service for the physicians, of the development of standards of diagnosis, of concerted efforts at environmental improvement and of the provision of adequate facilities for treatment.

It is necessary for success that the initiation of such a plan should be desired by and originate within the community.

A central "planning committee" made up of representatives of the health department, the medical society, the public health nursing, the parent-teachers association, various health and voluntary social agencies and the schools and youth organizations should assist an executive committee in the matters of public health and epidemiology, treatment and professional instruction and public information and finance.

DAVIS, Rochester, N. Y.

COLD HEMAGGLUTININS IN VISCERAL LEISHMANIASIS (KALA-AZAR). H. M. ROSE, Proc. Soc. Exper. Biol. & Med. **58**:93 (Jan.) 1945.

Cold agglutinins, or autoagglutinins, varying in titer from 1 to 128 and from 1 to 1,024, respectively, were found in 2 patients (a 15 year old girl and 23 year old man) proved to have Leishman-Donovan bodies, whose symptoms disappeared with the administration of Neostibosan (diethylamine para-aminophenylstibinate). The serums of 300 normal subjects and of patients suffering from a variety of diseases showed practically no cold agglutination. In the girl the cold agglutination was found to disappear when the patient had recovered.

HANSEN, Galveston, Texas.

Chronic Infectious Diseases

SYPHILIS TRANSMITTED FROM A CONGENITALLY SYPHILITIC CHILD TO HIS OWN FATHER. HOLLIS INGRAHAM and ALFRED HESSE, Am. J. Syph., Gonor. & Ven. Dis. **28**:733 (Nov.) 1944.

The authors report the transmission of syphilis from a mother to her child in utero and from the child after birth to the father, by contamination of his conjunctiva. White petrolatum which was applied to the child's nose for treatment of a syphilitic rhinitis was also applied from the same container by the father about his own nose; therefore it seemed to be the likely source of the father's infection.

REUTER, Milwaukee. [ARCH. DERMAT. & SYPH.]

Diseases of Blood, Heart and Blood Vessels and Spleen

CHOLELITHIASIS IN SICKLE CELL ANEMIA. H. STEPHEN WEENS, Ann. Int. Med. **22**:182 (Feb.) 1945.

Four cases of sickle cell anemia in which gallstones were demonstrated roentgenologically are reported. One of the patients was a child. A review of the literature revealed that the patients had gallstones in twelve out of forty-four

autopsies performed in cases of sickle cell anemia. All patients were in the age group below 40, in which cholelithiasis is infrequent.

READING, Galveston, Texas.

HEART DISEASE IN CHILDREN FROM THE PEDIATRIC VIEWPOINT. S. F. MORGAN, Wisconsin M. J. **44**:676 (July) 1945.

The pediatrician must be on the lookout for the "prerheumatic" child, the child in whom there is a physical state which gives favorable soil for the development of rheumatic fever. This state may be characterized by easy fatigability, unexplained episodes of fever and failure to gain proper weight. Adequate care of these children and of children with acute infections will help to prevent first attacks of rheumatic fever. A diagnosis of rheumatic fever should not, however, be made by a process of elimination without sufficient evidence to support the diagnosis. Prolonged fever and rapid sedimentation rate do not in themselves justify the diagnosis.

BAIRD, Wauwatosa, Wis.

STUDIES ON PROTHROMBIN: A COMPARISON BETWEEN PREMATURE AND FULL TERM INFANTS. J. HENNING MAGNUSSON, Ann. pædiat. **163**:105 (Aug.-Sept.) 1944.

A report is made in this paper of a study of the behavior of the prothrombin in infants weighing 2,500 Gm. or less at birth. The earlier investigations of the prothrombin content of premature infants are described and discussed.

The prothrombin content was determined for 95 premature infants during the first four weeks of life. For each of these infants, a full term baby born at the same time was selected and the trend of its prothrombin level followed. The number of full term infants examined was 94.

A comparison between the premature and the full term infants showed that the prothrombin level of the former group was lower on the first and second days of life. Thereafter, this feature could not be definitely established, despite the fact that the prothrombin level of the premature infants, from the standpoint of the actual figures, was lower after this time. At the two week determination, however, the level in the premature babies was so much lower (a statistically significant difference) that it must be assumed that a lability in the regulation of the prothrombin is still in existence in these infants at this stage of life.

A group of premature infants and a group of babies born at term, of approximately the same size, received a vitamin K preparation at birth. The prothrombin content was determined during the first week of life. In both instances a fully adequate effect was obtained from this therapy. With the exception of the first and the fourth days, the premature infants, however, had a lower prothrombin level than the full term babies.

The quantity of prothrombin in the blood of 6 premature infants whose condition proved to be wholly or partially resistant to vitamin K treatment during the first days of life is illustrated in diagrammatic form. One of these babies also had a comparatively low fibrinogen content during the first week of life.

The factors likely to have been of significance in causing the peculiarities observed in this investigation respecting the regulation of the prothrombin in the blood of the premature infants are discussed. The prothrombin content was determined for a number of mothers of both premature and full term infants. No difference between the two groups was discovered. The effect of the type of feeding on the prothrombin content in the blood is discussed on the basis of a series examined by the present writer consisting of 32 full term infants who were given comparatively large amounts of breast milk during the first days of life.

AUTHOR'S ABSTRACT.

Diseases of Nose, Throat and Ear

AN INTERBEHAVIORAL ANALYSIS OF SEVERAL ASPECTS OF STUTTERING. HARRIS HILL, J. Gen. Psychol. **32**:289, 1945.

This discussion places stuttering behavior in an interbehavioral framework, the organism, with its historical backgrounds interacting with objects, conditions or activities in a particular field, constituting the subject matter of such a study. The author believes that the blocks manifested in stuttering are occasioned originally by direct stimulation, either by difficulty in pronunciation or in finding words or by interruptions induced by affective and emotional reactions. Such blocks become substitute responses as conditioning develops. In order to understand the learning of stuttering the author inspects the attention, perception and consummatory responses of the stutterer, the feelings and emotional behavior and the relationship to the person spoken to and the object spoken about.

POLLACK, Evanston, Ill. [ARCH. OTOLARYNG.]

TREATMENT OF VINCENT'S ANGINA. CLARENCE PORTER JONES, Laryngoscope **55**: 147 (March) 1945.

Vincent's angina is probably due to multiple or mixed infection: the spirilla, the fusiform bacilli and various cocci.

In the diagnosis, syphilis and granulocytopenia should be ruled out. A smear and cultures should be made. Absence of spirilla or of fusiform bacilli from a smear does not preclude their presence in the throat. Some of the points in Jones's treatment follow. The lesion is cleaned and inspected, and a 2 per cent solution of a cocaine salt is applied. The blood is tested, and 0.45 Gm. of neoarsphenamine is injected intravenously. Sulfathiazole in the form of a gum or lozenges is used locally. Codeine, acetylsalicylic acid and vitamin C are given internally. More neoarsphenamine is given if improvement is not rapid. Jones has had better and quicker results with this than with any other form of treatment.

HITSCHLER, Philadelphia. [ARCH. OTOLARYNG.]

THE SPEECH HANDICAPPED. WENDELL JOHNSON, Rev. Educ. Research **14**:241 (June) 1944.

Johnson finds that the estimates of the number of children with defective speech in the public schools in the United States vary according to the definitions and the methods of survey used and that there are more boys than girls with defective speech. He finds that children with defective speech present all levels of intelligence but that more of them show a subnormal level. According to the studies made before 1941, children whose speech was defective were more retarded scholastically than their intelligence levels warranted, but since 1941 investigators have found that there is no such retardation. Although correction of speech in the United States has been developed through the public schools, only a small percentage of the needy pupils are given treatment. The author states that many textbooks and articles on correction of speech have been published recently. There has been increased research in the field of disorders of speech, especially in that of the development of speech and language, of the interrelation of speech and hearing and of language behavior. The field of the pathology of speech has been extended in the past few years by research, and a number of authors and investigators are mentioned. The article is well documented and annotated.

FERGEN, University, La. [ARCH. OTOLARYN.]

Diseases of Lungs, Pleura and Mediastinum

UNUSUAL PLEURAL EFFUSIONS. SOL KATZ and HAROLD R. REED, Radiology **45**:147 (Aug.) 1945.

Pleural effusions free in the pleural cavity or isolated in small areas in the pleural cavity or in the interlobar spaces are discussed, and eighteen illustrations are furnished by the authors, demonstrating the unusual positions and contours that may be assumed as well as the diagnostic confusion that may arise. Fluoroscopic examination and roentgenograms made in a variety of positions are mandatory for proper and complete evaluation in these cases.

ANSPACH, Chicago.

MEDIASTINAL EMPHYSEMA. R. L. FLETT, J. Laryng. & Otol. **59**:235 (July) 1944.

In the case reported, mediastinal emphysema developed twenty-four hours after removal of the tonsils and adenoids, which was followed by reactionary nasopharyngeal bleeding. Subsequent bronchoscopy revealed a check valve obstruction of the right main bronchus due to a blood clot. This was removed by suction, with immediate improvement in regard to cyanosis and dyspnea. The rather high temperature gradually receded over five days, as did the surgical emphysema, which at one time had appeared in the base of the neck, in the angles of the jaw, over the upper part of the chest and in the axillas. Roentgenograms of the chest made prior to bronchoscopy had shown air in the mediastinum and the neck with cardiac displacement to the left. On the fifteenth day after bronchoscopy roentgen examination revealed a return to normal. The patient was discharged from the hospital on the twenty-fourth day after operation.

An excellent study of mediastinal emphysema from the point of view of pathology, as well as a review of cases reported by others, is included. In the case reported it was decided that there had been ballooning of the right lung due to the valvular obstruction of the right main bronchus, which resulted in alveolar rupture and spread of air through the interstitial tissue of the lung to the hilus and the mediastinum. The author concludes that postoperative aspiration of blood from the nasopharynx may be considered as a possible common cause for abscess of the lung following adenotonsillectomy.

LEJEUNE AND STEELE, New Orleans. [ARCH. OTOLARYNG.]

LOBAR PNEUMONIA IN CHILDREN WITH SPECIAL REFERENCE TO TREATMENT. T. F. SU and B. C. LEE, Chinese M. J. **62**:270 (July-Sept.) 1944.

Many of the children of Shanghai commonly have lobar pneumonia; in the three years from 1938 to 1941 there were reported 105 cases typical in clinical character and confirmed usually by roentgenologic reports. The seasonal incidence of greatest frequency was in February and March, and the disease was commoner in infants under 1 year than in any other one year age group. The right lung was more often affected than the left, but the lower lobe of the left lung was the single lobe most often involved.

Sulfonamide compounds were used in 56 cases, chiefly sulfapyridine, with fairly high toxic reactions; sulfathiazole was given in a few instances. For 30 children cultures of the sputum and of the chest fluid were made, and nearly all showed pneumococci. As a whole, the febrile period was shortened.

NEFF, Kansas City, Mo.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL MALFORMATIONS OF THE ANUS AND RECTUM. EUGENE T. DMYTRYK, Arch. Surg. **50**:253 (May) 1945.

Congenital malformations of the anus and rectum are rather uncommon and are said to occur about once in every five thousand newly born babies. Such anomalies are classified by Ladd and Gross into four types, as follows:

1. Incomplete rupture of the anal membrane or stenosis at a point 1 to 4 cm. above the anus.
2. Imperforate anus with the obstruction due only to a persistent membrane.
3. Imperforate anus with the rectal pouch separated from the anal membrane.
4. Normal anus and anal pouch with the rectal pouch ending blindly.

The author studied 15 patients with congenital malformation of the anus and rectum. In this group of patients only two of the four types of anomalies were represented. For all patients, surgical treatment was employed. There was no mortality in the cases of incomplete rupture of the anal membrane, but there was 70 per cent mortality in the cases of imperforate anus with the rectal pouch separated from the anal membrane.

KAISER, Rochester, N. Y.

ACUTE APPENDICITIS IN CHILDHOOD. H. WILLIAM SCOTT JR. and PAUL F. WARE, Arch. Surg. **50**:258 (May) 1945.

The authors reviewed the cases of 506 children with acute appendicitis treated at The Children's Hospital in Boston since 1939 and compared them with those of the 848 patients treated during the ten years prior to 1939. A complete statistical study is made of all factors bearing on the illness, such as age, duration of symptoms, temperature, blood count and spasm of the rectus muscle. The treatment is discussed with special reference to perforative appendicitis. The authors stress that it is the policy of their clinic to individualize the preparation of children with appendical peritonitis or abscess for operation, delaying appendectomy only for the brief period necessary to obtain the maximum benefit from supportive measures.

A comparison of mortality rates in the present series with those of the preceding ten year period is presented. The over-all mortality rate has been reduced by approximately 50 per cent, and the recent percentage of fatalities in cases of perforated appendicitis is actually lower than the over-all rate of the earlier group of patients. The factors responsible for the improvement in treatment include more adequate preoperative preparation, early appendectomy and a better standardized postoperative regimen, including routine gastric suction, Fowler's position and parenteral administration of fluids, with the addition of sulfadiazine in cases of perforation.

KAISER, Rochester, N. Y.

AN UNUSUAL ILEOILEAL INTUSSUSCEPTION. MILROY PAUL, Arch. Surg. **50**:307 (June) 1945.

A 4 year old boy had an intussusception that started after treatment for round worms. The unusual factor in this case was the presence of a double-barreled loop of bowel within the sheath of the intussusception. Operation completely relieved his symptoms.

KAISER, Rochester, N. Y.

ABDOMINAL PAIN IN CHILDREN FROM A SURGICAL STANDPOINT. ALFRED STRAUSS, J. A. M. A. **128**:330 (June 2) 1945.

The diagnosis of acute abdominal conditions in children is difficult owing to the differentiation to be made between surgical conditions and manifestations of acute medical conditions, the anomalies which are found in the abdomen and the difficulty of palpation and percussion of the abdomen. The author says:

"Early diagnosis and operation are the important factors for lowering the mortality rate of appendicitis in children, and more harm can result from the delay of operations than from operations performed on an erroneous diagnosis."

BAIRD, Wauwatosa, Wis.

PROBLEMS IN THE SURGICAL TREATMENT OF CONGENITAL MEGACOLON. RAWLEY M. PENICK JR., J. A. M. A. **128**:423 (June 9) 1945.

Before surgical intervention is recommended for treatment of congenital megacolon the diagnosis must be established by history and by roentgenographic studies showing persistent dilatation in the absence of mechanical obstruction. Failure of response to medical treatment, including the use of mecholyl bromide or syntropan, should be demonstrated. Failure of response to spinal anesthesia is not a contraindication to surgical intervention, but it may be an omen of failure. Surgical treatment is usually contraindicated for patients less than 2½ years of age.

Sympathectomy in the left lumbar region gave good results in 7 of 11 cases. Three patients were greatly improved. In 1 case the operation was a complete failure.

BAIRD, Wauwatosa, Wis.

PENICILLIN TREATMENT OF ORAL INFLAMMATIONS IN CHILDHOOD. M. B. MARKS, J. Pediat. **26**:582 (June) 1945.

The usual treatment of thrush, Plaut-Vincent's infection and herpetic stomatitis with gentian violet medicinal, irrigations with boric acid and peroxide, and with sodium perborate and glycerite of boroglycerin suffices in most cases. However, for severe infections the treatment is long and tedious and is trying both to the pediatrician and to the patient. In these cases, the use of penicillin, both topically and by injection, is invaluable because of the rapidity with which it brings about an amelioration of symptoms. Ten thousand to 20,000 units of penicillin is injected intramuscularly every three hours, depending on the age of the child and the severity of the infection. For small infants a total dose of 40,000 to 50,000 units is all that is necessary. For older children the total dose is usually 100,000 units. A greater amount may be employed when it is thought necessary, but in the author's experience the total dose stated seems to be adequate.

For young infants or for older children when it is not desirable to carry out the injection technic penicillin may be used topically in a concentration of 250 units per cubic centimeter. In this method, the solution is applied with swabs and loose cotton packing to the affected gums and buccal surfaces. Although the results are a little slower than with the intramuscular route, they are as good, and certainly the method is more effective than the former procedures of using dyes, oxidizing reagents and mild and strong antiseptics.

For particularly severe infections a combination of both the topical and the injection technic may be carried out. The intramuscular route should be preferred in the administration of penicillin. It is seldom that more than four or five deep injections are required, and these can be given within a period of twelve to fifteen hours.

From an experience in treating a number of infants and children with the oral manifestations of thrush, Plaut-Vincent's infection and herpetic stomatitis, Marks is convinced that penicillin now supersedes all hitherto employed remedies as being the most reliable and effective.

AUTHOR'S ABSTRACT.

TREATMENT OF LYE STRICTURE OF THE ESOPHAGUS. DAVID H. JONES, Laryngoscope **55**:133 (March) 1945.

Jones believes that the esophagus with lye burns is best treated by early and frequent dilation. This should be done long before any apparent strictures have formed. This is in contrast to the older treatment, in which dilation was not employed until after strictures were present. A case is presented.

HITSCHLER, Philadelphia. [ARCH. OTOLARYNG.]

RECURRENT INFECTIOUS PAROTITIS. T. HALBERTSMA, Ann. pædiat. **163**:75 (Aug.-Sept.) 1944.

The symptoms of recurring infectious parotitis are discussed from 2 personal observations. In both cases, streptococci were obtained from the salivary fluid; peculiarities of the blood count were the high values found for the eosinophils (13 and 10 per cent respectively), no cause therefor being conceived. The value of the sialogram is stressed, which in these cases plainly showed the symptoms of inflammation of the duct, as demonstrated in the roentgen pictures given.

AUTHOR'S ABSTRACT.

Nervous Diseases

KERNICTERUS UNASSOCIATED WITH ERYTHROBLASTOSIS FETALIS. FRANCIS M. FOSTER and RAYMOND A. MCCORMACK, J. Neuropath. & Exper. Neurol. **3**: 379 (Oct.) 1944.

Foster and McCormack report their studies on 2 patients with kernicterus. In 1 Negro boy severe jaundice developed thirty-six hours after delivery, followed by opisthotonos and rigidity. He died five days after birth. The parents were healthy, and the three preceding pregnancies had resulted in three viable female children. Both parents were Rh positive. The other Negro boy, a first born of syphilitic parents, presented severe jaundice on the fourteenth day and died on the fifteenth day. The mother had received antisyphilitic therapy, beginning in the sixth month of pregnancy. Both parents were Rh positive. Necropsy was performed in both cases.

Foster and McCormack state that the cause of the severe icterus of the newborn in these 2 cases is not evident. Erythroblastosis fetalis is ruled out by serologic studies, blood smears and autopsy.

GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Psychology and Psychiatry

SCHIZOPHRENIA IN A FOUR YEAR OLD BOY. H. ROBERT BLANK, OLIVE CUSHING SMITH and HILDE BRUCH, Am. J. Psychiat. **100**:805 (May) 1944.

Blank, Smith and Bruch report studies on a 4 year old boy with schizophrenia. The family history revealed an extensive psychopathic trend. The home atmosphere was crowded with fears and terrors, and the mother was almost as sick as the patient. The early development was normal, but there was a gradual development of seclusiveness, terrors, apathy and temper tantrums. Examination revealed that the patient was aloof, preoccupied and self absorbed, while productivity was sparse. In observed play there was more urgency, and laughter became increasingly shrieking and excited. During the course of nine months' study in group situations, the patient was found to be passive, dependent and seclusive; the productions showed echolalia and jargon manifestations, and contact was transitory. Early in the course of therapy some catatonic features and faulty toilet habits were present. On retiring, he babbled incoherently for long periods and had night terrors. At the time of discharge a happy adjustment had been made at a simple level, but the child remained a withdrawn, blocked and passive personality.

The authors evaluate the familial interpersonal relationships in this case and conclude that the child's symptoms might be considered as defensive stratagems yielding him protection from a threatening world.

FORSTER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Ductless Glands; Endocrinology

GOITER STUDIES WITH THE RAT. A. W. HALVERSON, JAMES H. SHAW and E. B. HART, J. Nutrition **30**:59 (Aug.) 1945.

The authors have reported a ration which produces an iodine deficiency in the white rat. Definite enlargement, redness and histologic changes were noted in the thyroid glands of the rats receiving the basal ration and those receiving the basal ration plus 0.5 microgram of iodine per rat per day. The addition of 1 and 2 micrograms of iodine per day to the basal ration largely corrected the glandular enlargement; and 2 micrograms resulted in almost complete prevention of pathologic changes. No differences in growth or food consumption were noted between the group receiving the basal ration and the group receiving the iodine supplements.

FREDEEN, Kansas City, Mo.

Diseases of the Eye

TRACHOMA VIRUS AND THE MORPHOLOGY OF INCLUSION BODIES. A. LOEWENSTEIN, Am. J. Ophth. **28**:282 (March) 1945.

Loewenstein summarizes his observations on advanced trachoma: The follicles consisted of lymphocytes, plasma cells, fibroblasts and macrophages (cystophages, Marchand). The macrophages contained no granules suggesting inclusion bodies. The caps reported by Cuenod in the cells of the follicles were not found in any of the 23 cases of advanced trachoma which formed the basis of this histologic investigation. The appearance of the inclusion bodies differed in scrapings and in section. In the scrapings they showed considerable polymorphism, and individual elementary and initial bodies might be found alone in the cells. In sections encapsulated inclusion bodies with many Giemsa staining elements were found in the superficial epithelial layers. In the middle layers they were fewer, and they were absent in the deeper layers. In the subepithelial tissues, reticulum cells of fibroblast character were filled with blue and purple granules. Granules were free in the tissues—some single, others in colony. The tarsus was found to be full of reticulum cells of fibroblast character, similar to those in the subepithelial tissues.

W. ZENTMAYER. [ARCH. OPHTH.]

COMPLETE CONGENITAL PIGMENTATION OF THE OPTIC DISC. W. MOEHLE, Am. J. Ophth. **28**:377 (April) 1945.

Moehle briefly reviews the literature and reports the case of a 65 year old man with chronic glaucoma, whose right optic disk was entirely covered with brownish black pigment.

W. S. REESE, [ARCH. OPHTH.]

RECURRENT JUVENILE PAPILLOMA OF THE CONJUNCTIVA. J. D. WALKER, Am. J. Ophth. **28**:751 (July) 1945.

Walker reports a case of papilloma of the conjunctiva which recurred repeatedly, eleven operations being performed during five years of observation and treatment. From the literature it is evident that a papilloma may not be an innocent growth, as a number of cases are reported which show that it is capable of malignant degeneration. The tumor is best removed surgically. If roentgen radiation or radium is used, every precaution should be used to protect the lens.

W. ZENTMAYER. [ARCH. OPHTH.]

CONGENITAL ARTERIAL ANEURYSM AT THE PAPILLA. FREDERICK H. THEODORE and WILLIAM H. BONSER, Arch. Ophth. **32**:492 (Dec.) 1944.

The anatomy of the optic papilla is so important that any deviations from the normal must be seriously considered. There is considerable confusion in the classi-

fication of aneurysms of the retinal vessels, and it is convenient to divide the lesions in the various cases thus far reported into three types: (1) aneurysms of the larger branches of the central retinal artery, all of which appear to have occurred secondary to vascular disease or trauma and which are generally associated with visual impairment; (2) miliary aneurysms, which are of two types, one essentially a senile degenerative phenomenon and the other neoplastic, and (3) arteriovenous aneurysms, which are essentially congenital in origin and are often without associated visual disturbances. The third category is of additional interest in that recent articles have called attention to the association of this striking anomaly with similar arteriovenous aneurysms in the skin and brain. The aneurysm in the case reported corresponded to none of these types but resembled the third in several important details, although the aneurysm was entirely arterial.

SPAETH, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

SCLERAL ABSCESS. F. M. LEE, Chinese M. J. **63**:60 (Jan.) 1945.

Lee reports 2 cases of scleral abscess. The first case was that of a boy aged 8 years. After an iridectomy the patient tore off the surgical dressings and rubbed the eye. The abscess developed one week later. In the second case, that of a young man, the abscess developed one month after an iridectomy.

W. ZENTMAYER. [ARCH. OPHTH.]

Skin Diseases; Allergy

HIGH DOSAGE VITAMIN C IN ALLERGY. SIMON L. RUSKIN, Am. J. Digest Dis. **12**:281 (Sept.) 1945.

From an extensive clinical investigation on 100 patients, the author makes the following conclusions:

First, ascorbic acid plays a valuable role in the treatment of nasal allergy, but it is useful fundamentally in large doses, ranging from a minimum of 250 mg. daily, with an optimum dose of 750 mg. daily.

Second, ascorbic acid is useful in allergy, administered either by the oral route or by injection.

Third, the results of the administration of ascorbic acid are, in general, advantageous to allergic patients, with or without desensitization.

Fourth, in some cases ascorbic acid therapy alone proved superior to pollen desensitization in previous years.

Fifth, allergic disturbances are related to nutritional deficiencies, primarily to a deficiency of ascorbic acid.

To supplement the clinical investigation, the author studied sections of New Zealand rabbits' lungs, kept in Ringer-Locke dextrose solution. The bronchiole to be studied was stretched out over an opening in a sheet of cork. The whole was kept in a Petri dish containing the Ringer-Locke dextrose solution, and the substances to be tested were added to this. The preparation was kept on a warm stage, and observations were made through a microscope.

Sodium ascorbate and ascorbic acid did not influence the speed of recovery from histamine contraction but did produce antagonism to the second dose of histamine hydrochloride.

Ephedrine sulfate caused slight inhibition of recovery from histamine hydrochloride, with little or no antagonism to the second dose of histamine. With ephedrine ascorbate, there was quick recovery from histamine. With ephedrine hydrochloride, there was an increase in histamine contraction and no histamine antagonism but, rather, constriction.

Calcium gluconate not only did not antagonize histamine hydrochloride but, in fact, increased contraction of the bronchiole in response to the drug. Calcium ascorbate, on the other hand, antagonized histamine, and the response was quicker than that either to ascorbic acid alone or to sodium ascorbate.

Amphetamine ascorbate produced a quick recovery from histamine contraction, with strong histamine block, but amphetamine sulfate showed no histamine antagonism and, in fact, prolonged histamine contraction.

There was a remarkable synergistic effect of ascorbic acid on epinephrine. The epinephrine ascorbate showed about twice the bronchiole-dilating capacity exerted by epinephrine hydrochloride and a much quicker and more active histamine antagonism.

LESLIE, Evanston, Ill.

ANGIOKERATOMA. E. LIPMAN COHEN, Brit. J. Dermat. **56**:228 (Nov.-Dec.) 1944.

The author reports a case of angiokeratoma (Mibelli) in a girl aged 16. For four years she had spots on her right leg. Two years after the onset she had roentgen ray treatments of the lesions, and they became gray and harder but were unchanged in size. On examination, the lower two thirds of both legs were reddish purple, and they felt cold to the touch. On the back of the right leg over the proximal end of the achilles tendon was a group of warty swellings, the biggest being ¾ inch (1.9 cm.) in diameter. Distal to the warty swellings and also on the calf were a few lentil-sized circumscribed discrete reddish purple macules. Treatment consisted of ingestion of ½ grain (0.03 Gm.) of thyroid daily and the application of solid carbon dioxide to the warty lesions. Improvement was steady, and the growths became gradually smaller, their warty tops eventually falling off.

According to the author, a search of the literature has failed to reveal any previous example of such lesions occurring on the back of the leg. In all previous cases of the disease the fingers, hands, toes or scrotum have been the sites of involvement.

BLUEFARB, Chicago. [ARCH. DERMAT. & SYPH.]

Miscellaneous

CYANOSIS IN INFANTS CAUSED BY NITRATES IN WELL WATER. HUNTER H. COMLY, J. A. M. A. **129**:112 (Sept. 8) 1945.

Two cases are reported of young infants with gastrointestinal disturbances whose cyanosis was due to methemoglobinemia caused by the high nitrate content of the contaminated well water used in their formulas. Reduction of the nitrate ion to the nitrite ion in the gastrointestinal tract, with absorption of the nitrite ion and oxidation of hemoglobin, was the mechanism of action. Boiling this water did not render it safe.

This report offers an explanation for previously unexplained cyanosis or cyanosis erroneously attributed to congenital heart disease.

Methylthionine chloride in doses of 1 to 2 mg. per kilogram relieves the cyanosis.

BAIRD, Wauwatosa, Wis.

ACCIDENTS DUE TO SULFONAMIDE THERAPY IN INFANCY AND CHILDHOOD. L. VELASCO BLANCO, Arch. am. de med. **19**:11 (Jan.-March) 1943.

The greater tolerance of infants and children in comparison to that of adults to sulfonamide drugs is pointed out. A general discussion on toxic manifestations, absorption and excretion, dosage, mode of administration and prophylaxis and treatment of toxic symptoms follows.

ABALLI, Habana, Cuba.

Book Reviews

Constitution and Disease: Applied Constitutional Pathology. By Julius Bauer, M.D. Second edition. Cloth. Price, $4.00. Pp. 247, plus 13. New York: Grune & Stratton, Inc., 1945.

The characteristic defect of American medicine is possibly the tendency to lay emphasis on the disease, the lesion and the laboratory test and to overlook "the patient as a whole." Accordingly, this book, which seeks to explain the European concept of the human constitution in the light of American medical thought, is both stimulating and unique.

The author writes in a fluent, almost colloquial, style. A purist, it is true, may object to such terms as "sexotropic" and "sicklemia" and must certainly object to the term "oculist" when applied to a physician who is called on to explain the cause of iridocyclitis. But these slips may be forgiven any former Viennese professor who spares the reader the ordeal of reading English words in a German sentence structure.

The constitution, as Dr. Bauer defines it, is the hereditary makeup of the individual as determined by his genes. This logical definition is rigorously followed. It leaves the reader, however, without a completely satisfactory term for the total individual, the resultant of all the genetic and all the environmental influences.

Geneticists, like environmentalists, tend to extreme partisanship, and the author does not wholly escape this defect. He explains obesity, for example, as "a unitary biologic process controlled by a particular gene or gene complex" and states, "Frankly, I do not believe that pure exogenous obesity exists at all." Most readers would be unconvinced by such evidence as the report that 73 per cent of a group of obese patients had one obese parent. Genes, it is true, run in families, but so does good cooking! Similarly, evidence for "constitutional biologic inferiority" of the thyroid is rather insubstantial if it must be supported by the statement, "In a case I observed, it is hardly coincidental that the grandmother died of a cancer of the thyroid gland and the granddaughter has an infantile myxedema."

In the classification of constitution the author is properly skeptical of the "status thymolymphaticus" but, unfortunately, gives extended treatment to his own invention, the "status degenerativus." This term could prove handy to any one in the heat of political argument, but it does not apply to any definite genetic entity. Hence, the "status degenerativus" provides a dignified way of evading scientific explanation but nothing more.

Such defects in the book as have been cited, however, are the exception rather than the rule. This compact volume brings together, examines and classifies what is known about the genetic factor in health and disease. It is well documented and well indexed. As human genetics emerges from the limbo into which Hitler's racial pseudoscience has forced it, Dr. Bauer's scholarly survey will be increasingly appreciated.

Implications of Nutrition and Public Health in the Postwar Period. Proceedings of a Conference Held at Detroit, 1944. Price, not given. Pp. 206, with 11 illustrations. Detroit: Children's Fund of Michigan, 1945.

The book consists of ten separate papers by different authors, covering different aspects of the field of nutrition in relationship to public health. These timely discussions by experts in their particular fields were presented at a conference sponsored by the Research Laboratory of the Children's Fund of Michigan, which has itself made many valuable contributions to knowledge, under the able directorship of Dr. Icie Macy Hoobler. The authors of four of the ten papers presented at the conference are pediatricians.

For any intelligent person wishing to acquire an accurate conception of the over-all relationship between food and health without the necessity of too extensive reading, no better source of information can be found than this little book. Such important subjects as those pertaining to the production, processing and distribution of foods, which are not ordinarily encountered in medical writings on nutrition, are covered in a scholarly manner. Some of the papers deal with the roles of particular nutrients, such as the vitamins, protein, individual amino acids and calcium, in their specific relationships to growth and development and immunity to certain disease states, but the main emphasis throughout the book is properly placed on the importance of completeness in the diet as a whole. The present tendency to substitute vitamin pills and highly refined foods for natural food products is decried.

The devastating effects of war on the nutrition of children in occupied countries are pointed out, and the need for dealing with the problem of food supply on an international scale is stressed as a potent factor in the preservation not only of health but of peace as well. An important practical point emphasized by one of the nonclinical speakers was that malnutrition is not always due to an inadequate food supply but in many instances has its origin in emotional or psychologic maladjustments in the home or at school.

Amigdalectomia y Enfermedad de Heine-Medin (Tonsillectomy and Heine-Medin Disease [Poliomyelitis]). By Hector Jose Vazquez. Price, not given. Pp. 48, with 10 tables. Buenos Aires, Argentina: Libreriá y editorial "El Ateneo," 1945.

In this booklet of forty-eight pages, the author gives an excellent review of the possible relation between tonsillectomy and anterior poliomyelitis. There is a discussion of the pathology and of the bibliography, including data from the work of Stillerman and Fischer (1938) and of Fischer, Stillerman and Marks (1941). The latter work is a report of the epidemic which occurred in Toronto, Canada, in 1937. The author's own experience with 100 selected cases in 1942 and 1943 is given in some detail. In 6 cases poliomyelitis occurred within thirty days following tonsillectomy and adenoidectomy and in 2 cases within eight weeks. He concludes that there is an etiologic relationship between the operation and the development of acute poliomyelitis and that when the latter develops, the symptoms occur predominantly in the upper portion of the nervous system.

The surgical procedure opens a portal of entry for the virus, which is unable to invade the tissues without this. Such a procedure may lower the local resistance enough to allow the virus, present as a saprophyte, to gain virulence in a medium most suitable for its development.

In addition, it is pointed out that in the procedure of administering local anesthesia the needle may carry the virus from the surface of the tonsil to the deeper tissues, thus reproducing in human subjects one of the experiments which Sabin carried out in monkeys.

It is advised that tonsilloadenoidectomy be postponed during an epidemic of poliomyelitis.

Las arthritis agudas supuradas en la primera infancia. By Manuel U. Diaz Bobillo. Paper. Price, not given. Pp. 125, with 19 illustrations. Buenos Aires, Argentina: Library editorial "El Ateneo," 1944.

This is a monograph on suppurative arthritis in infancy and childhood based on the author's experience in 27 instances. He concludes that the disease is uncommon in children and that the Pneumococcus is the most frequent etiologic organism, followed by the Staphylococcus, streptococcus and gonococcus. The condition usually is preceded by lesions elsewhere in the body. The prognosis is good, and the only complications are subluxation of the joint, although if the suppuration occurs in the hip joint there may be destruction of important structures. The medical treatment is with sulfonamide compounds, and the surgical is immobilization with puncture or, if necessary, a simple incision.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. H. P. Wright, 1414 Drummond St., Montreal.
Place: New York. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff and Dr. Donald Paterson, Hospital for Sick Children, Great Ormond St., London, W. 1.
Place: Rugby School, Rugby. Time: Aug. 1-3, 1946.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

SOCIEDAD DE PEDIATRIA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texidó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.
Place: San Francisco. Time: July 1-5, 1946.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Time: Jan. 15-18, 1946.
Region I. Place: Hotel Pennsylvania, New York. Time: April 2-4, 1946.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. C. Anderson Aldrich, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis 8.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.
Place: Banff, Alberta. Time: June 14-15, 1946.

Society for Pediatric Research

President: Dr. Edward M. Bridge, 219 Bryant St., Buffalo, N. Y.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia 46.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.
Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. William P. Buffum, 122 Waterman St., Providence, R. I.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Place: Banff, Canada. Time: June 11, 1946.

Northwestern Pediatric Society

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.
Place: Birmingham. Time: September 1946.

Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.
Place: Biltmore Hotel, Los Angeles. Time: May 7-10, 1946.

Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Ruskin King, 10 W. Taylor St., Savannah.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Two meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 18, 1946.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Hotel Pennsylvania, New York. Time: May 2-3, 1946.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: September 1945.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Arthur H. London Jr., 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, Duke Hospital, Durham.
Place: Variable. Time: Sept. 9, 1946.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–30th St., Oakland.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Lonita Boggs, 300 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, 429 Wade Hampton Office Bldg., Columbia 10.
Place: Poinsett Hotel, Greenville. Time: May 2, 1946.

TEXAS PEDIATRIC SOCIETY

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.
Place: Fort Worth. Time: October 1946.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.
Place: Huntington. Time: May 13-15, 1946.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 511 United Bank Bldg., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Bronx Pediatric Society

President: Dr. Walter Levy, 12 E. 88th St., New York.
Secretary: Dr. Joseph Blasenstein, 960 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lambert Krahulik, 14 Sidney Pl., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m. fourth Wednesday of February, March, April, May and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Louis W. Sauer, 636 Church St., Evanston, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Theodore K. Selkirk, 3605 Edwards Rd., Cincinnati.
Secretary: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. O. René Caillet, 4325 Cole Ave., Dallas, Texas.

Secretary-Treasurer: Dorothy Wyvell, Bradford Memorial Hospital for Babies, Texas.

Place: Children's Medical Center. Time: 1 p. m., fourth Saturday and 8:30 p. m. the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Philip J. Howard, 2977 W. Grand Blvd., Detroit, Mich.

Secretary: Dr. John C. Montgomery, 564 Fisher Bldg., Detroit 2, Mich.

Place: Variable. Time: Five times a year.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.

Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.

Place: River Oaks Country Club. Time: 7:30 p. m., fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.

Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.

Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Milo B. Brooks, 1033 Gayley Ave. W., Los Angeles.

Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.

Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Abraham M. Litvak, 1145 Eastern Parkway, Brooklyn.

Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.

Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m. fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02–91st Ave., Queens Village, N. Y.

Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.

Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. William F. O'Donnell, 2701–28th St. N. W., Washington, D. C.

Secretary-Treasurer: Dr. Dorothy S. Jaeger-Lee, Children's Hospital, Washington, D. C.

Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.

Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

Place: Memphis Country Club. Time: 8 p. m., Dec. 13, 1946.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.

Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.

Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred E. Fischer, 73 E. 90th St., New York.

Secretary: Dr. Robert O. Du Bois, 122 E. 76th St., New York.

Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.

Secretary: Dr. Jeanne McKinnon-Shotstall, 625½ N. W. 10th St., Oklahoma City.

Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Ruth Hartley Weaver, 1719 Rittenhouse St., Philadelphia.

Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.

Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and May.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.

Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.

Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.

Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.

Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.

Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.

Time: Second Thursday of each month from October to May, inclusive.

SEATTLE PEDIATRIC SOCIETY

President: Dr. D. M. Dayton, 740 St. Helens Ave., Tacoma.

Secretary: Dr. W. B. Chesley, 1306 Madison St., Seattle 4.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. William Belford, 420 Walnut St., San Diego, Calif.

Secretary: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.

Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Park Bradshaw, Muskegon, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.